Author's response to reviews

Title: Is tinnitus in normal-hearing patients accompanied by hemifacial spasm also a type of hyperactive neurovascular compression syndrome? A magnetoencephalography study

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Author's response to reviews: see over
Dear editors:

Thank you for your comments on our manuscript entitled “Is tinnitus in normal-hearing patients accompanied by hemifacial spasm also a type of hyperactive neurovascular compression syndrome? A magnetoencephalography study” (MS: 9145537908745911). All authors reviewed the work and discussed about your concerns and attempting to address all of your comments. We would like to resubmit a revised version of our manuscript.

The revision details are as follows:

**Reviewer: 1**

*Comments to the Author*

[1] “Contralateral tinnitus associated with hemifacial spasm (HFS) is not uncommon, and is seen in approximately 7% of patients with HFS.” The cited study investigated 114 patients and found tinnitus on the SAME side (IPSILATERAL) in 7 of these patients. That comes to a percentage of 6.1% rather than 7%. It should also not be concluded from a single study, that tinnitus in HFS patients IS not uncommon. Perhaps one could write: MAY NOT BE uncommon, and was encountered in 7 of 114 HFS patients in a series by Ryu et al. (1998).

As reviewer commented, we described the prevalence of tinnitus accompanied with hemifacial spasm too definitely. However, there are few studies regarding the prevalence of this condition, currently available, we sited only one article about this issue. We changed the sentence as below reflecting reviewer’s comment.

Interestingly, there are some patients with ipsilateral tinnitus associated with hemifacial spasm (HFS), and this type of tinnitus was encountered in 10 of 142 patients with HFS in a series by Ryu et al.[6]

[2] It is also not sustainable that “If tinnitus is accompanied by HFS, surgical outcome following microvascular decompression is GENERALLY acceptable, especially in cases in which the cochlear nerve is affected.” if this conclusion is based on a single study (which reported improvement of tinnitus in 8 of the 10 patients studied).

There are two article about the surgical outcomes of microvasuclar decompression for tinnitus accompanied by hemifacial spasm. Although these two article described favorable surgical
outcome, it may not be general outcomes even for this type of tinnitus. We removed the word, ‘generally’, and added another reference following reviewer’s comment.

[3] Finally in this paragraph, I suggest to rephrase this sentence: Therefore, some types of tinnitus, but not all, have similar pathophysiology as HFS. This suggests that some particular forms of tinnitus may be caused – like HFS - by microvascular compression in the cerebellopontine angle.

This statement should be supported by citations from authors like de Ridder and Moller such as:

We have changed the sentence and added citation according to the viewer’s comment as below;

This suggested that some particular forms of tinnitus may be caused – like HFS - by neurovascular compression in the cerebellopontine angle.[8, 9]

[4] Thus, we postulate that the pathophysiologic mechanism of tinnitus accompanied by HFS is different than that of tinnitus alone.”

This postulation is easily challenged by the argument that in HFS an offending vessel has already been confirmed that runs very close to the vestibulocochlear nerve. The improvement in outcome for tinnitus in these patients may simply be the result of a better patient selection rather than the result of a different pathophysiological process.

The reviewer pointed out very important factors affecting surgical outcome. Although there is still possibility that different surgical outcome might be resulted from different pathophysiological mechanism, the difference of patient’s selection also could affect to the surgical outcome, as reviewer commented. We changed the sentences as below;

This better surgical outcomes may be resulted from the differences of the patient’s characteristics of that the patients with HFS had already confirmed offending vessel that run very close to the cochlear nerve. However, considering that other series of microvascular decompression for the patients without HFS also confirmed a neurovascular conflict on magnetic resonance imaging, it may also be postulated that the pathophysiologic mechanism of tinnitus accompanied by HFS is different than that of tinnitus alone.

[5] MEG results of AEF for patients in our series with tinnitus accompanied by HFS showed simultaneously increased auditory cortical activity and decreased N100m latency compared with patients with HFS without tinnitus (Table 1). This result suggests that tinnitus accompanied by HFS is likely not a type of hyperactive neurovascular compression syndrome, which typically shows simultaneously decreased nerve conduction velocity and cranial nerve function due to demyelination of the cranial nerve.[3]
Recently, a study was published about normal hearing patients with tinnitus. The authors observed shortening of I-V latency and enlarged Na and Pa amplitudes in an electrophysiologic study, and concluded that the cause of tinnitus in these patients seemed to have originated in the central nervous system.[13] Although the patients of that study did not have HFS, the other conditions regarding tinnitus were similar to the patients in our series, and this study suggested that the tinnitus in the patients in our series may have originated in the central nerves system, rather than the cranial nerve or the root entry zone."

Again, the conclusion is not readily sustained by data. If tinnitus resolved in 7 of 10 patients in one study after microvascular decompression of the facial nerve which is the closest neighbour of the cochlear nerve, one would logically assume that both disorders had the same cause: a compression of the cranial nerve or its root entry zone. The latter, by the way, is very close to the dorsal cochlear nucleus, a structure that the author point to as a “strong candidate for the origin of tinnitus” in the next sentence.

Moreover, if the I-V latency of the BAEP is shortened in patients with tinnitus, the pathophysiologic mechanisms to cause this disorder may be located all along the cochlear nerve (hyperconductivity) to the inferior colliculus, not to the least ruling out a more peripheral component, e.g. at the root entry zone.

As reviewer commented, our data from MEG study may not distinguish the mechanism of hyperactivity of central auditory nervous system. Initially we postulated that the pathophysiological mechanism of this type of tinnitus could have similar pathophysiological mechanism of other type of hyperactive neurovascular compression syndrome; chronic pulsatile compression of root exit zone – demyelination of cochlear nerve axon – ephaptic transmission. However, the MEG data from our study did not support this postulation. Therefore, we assumed that the activity of central auditory nervous system might be one of the main factors causing this type of tinnitus regardless of the cause of hyperactivity. We changed the paragraph as below;

Initially, we assumed that the pathophysiological mechanism of tinnitus accompanied by HFS might be quite similar to the two suggested pathophysiological mechanism of hyperactive neurovascular compression syndrome; 1) ephaptic transmission or 2) hyperactive cranial nerve nucleus and/or higher brain structure. If tinnitus accompanied by HFS is originated from ephaptic transmission of cochlear nerve, MEG for these patients should showed decreased auditory cortical activity and delayed latency from auditory stimulus and cortical evoked field. However, MEG results of AEF for patients in our series with tinnitus accompanied by HFS showed simultaneously increased auditory cortical activity and decreased N100m latency at the symptoms side compared with patients with HFS without tinnitus (Table 1). This result suggests that tinnitus accompanied by HFS is likely not caused by the ephaptic transmission of cochlear nerve by neurovascular conflict, and hyperactivity and hyperconductivity of
central auditory nervous system may play a key role for the pathophysiological mechanism. [10]

[6] Furthermore, control of HFS, regardless of treatment with microvascular decompression or botulinum toxin injection, is expected to be sufficient for relieving tinnitus in normal-hearing patients with HFS.”

Only if this speculation is supported by data in the future, the far-fetched assumptions in the discussion of the present study may hold some truth.

As long this is not shown, the authors should abandon the path of speculation for once, and deliver as many data as the authors possibly can. Most particularly, this regards the data on the outcome of the treatment of their patients. Has the tinnitus resolved after MVD for HFS? Has HFS resolved? Have any of the patients received botulinum toxin injections before undergoing surgery for HFS?

Thank you for good comments. We agree to your opinion that the assumption of causal relationship between facial sensory stimuli and tinnitus was far-fetched in some degree. If we want to definitely insist the causal relationship, we should also study about the treatment outcome of tinnitus by botulnnum toxin injection. However, because of the relatively small sample size, we could not present the evidence for this postulationin this study. Combining above, we changed the paragraph as below:

Combining our MEG results and above recent theory, hyperactivity of dorsal cochlear nucleus can be one of the major pathophysiological mechanisms of tinnitus accompanied by HFS. In our series, two of eight patients (12.5%) with tinnitus accompanied by HFS were continuously suffered from tinnitus even though no evidence of facial spasm after microvascular decompression. This outcome was comparable to the previous report that tinnitus of two of ten patients (20%) were unchanged after successful microvascular decompression for HFS, although the hearing function of some patients in previous series was already decreased before surgery.[6] If the tinnitus of all patients in our series were caused by the hyperactive dorsal cochlear nucleus induced by continuous facial sensory input, the tinnitus should disappear after control of facial spasm. However, even though small portion, some patients continuously suffered from tinnitus after successful microvascular decompression for HFS. On the other hands, if the hyperactivity was caused by the vascular conflict of dorsal cochlear nucleus, the tinnitus also should resolve after successful microvascular decompression, although some patient with neurovascular conflict syndrome example for HFS or trigeminal neuralgia still had their symptom after complete decompression of cranial nerve root exit/entry zone. Irreversible change of central auditory nervous system may be contributed to these patients, and further study might be helpful for understanding this change.

Another consideration for understanding the pathophysiological mechanism of tinnitus accompanied HFS is the reason of hyperactivity of central auditory nervous system. Hyperactivity of dorsal cochlear nucleus can be induced by both neurovascular conflict and multi-sensory input from facial sensory. In our study we could not conclude which factor had more influenced to this hyperactivity. Further clinical trial by controlling facial sensory input without microvascular decompression example for botulnnum toxin injection is expected to give answer for the main factor causing central auditory hyperactivity.

[7] Following MEG analysis of patients, we conclude that the origin of tinnitus in these patients with HFS is not the cranial nerve or root entry zone but the central nervous system, and control of HFS may be sufficient to relieve tinnitus. Further investigation and clinical correlation are required to obtain more information.”
As stated before, this conclusion is not validated by the data of the study. For all we can say, these patients show abnormal dipole strength and peak-latency in the hemisphere contralateral to auditory stimulation. Since the stimuli were acoustic, the whole auditory system – from the tympanic membrane to the auditory cortex - was involved in signal transmission and transformation. All along this pathway pathomechanisms may be located that, in the end, have caused change in the cortical MEG response.

We agree to the reviewer’s comments, and removed the sentences pointed out by the reviewer and changed as below;

The pathophysiologic mechanism of normal-hearing tinnitus accompanied by HFS is still controversial. Following MEG analysis of patients, we conclude that the origin of tinnitus in patients with HFS may be not the cranial nerve but the central auditory nervous system.

[8] The last sentence of the conclusion has been very wisely put: We should wait with clinically relevant conclusion until we have seen appropriate data.

We added the sentence that reviewer recommended as below;

Further investigation and clinical correlation are required to obtain more information, and we should wait with clinically relevant conclusion until we have seen appropriate data.

Reviewer: 2

[1] Authors do not consider the issue of pulsatile tinnitus that is a type of tinnitus reported in several cases of neurovascular compression. The pathophysiology of pulsatile tinnitus due to vascular compression is obviously different to that of other types of tinnitus. Also, intermittent clicking is heard ipsilaterally in some cases of hemifacial spasms. In these cases the stapedius muscle may be affected.

There are many symptom-type of tinnitus and the causes also vary according to the type of tinnitus. As reviewer commented, pulsatile tinnitus have different pathophysiological mechanism from other types of tinnitus, and stapedius muscle contraction related to facial nerve activation caused by hemifacial spasm also result in tinnitus-like symptom, although this is not true tinnitus but called as ‘tympanic noise’. We added this issue to the manuscript as below;

Tinnitus is defined as the subjective perception of a sound in the absence of any physical sound source. It could be the result of a spontaneous and aberrant neural activity of auditory system, and 5-15% of population in western society are known to experience chronic tinnitus- conventionally more than six to twelve months.[1] Because tinnitus is usually coincided with various ear disorders, surgical treatment of chronic tinnitus is mainly focused on ontological surgery. However, some types of tinnitus such as pulsatile tinnitus are known to be possibly caused by vascular compression, and different therapeutic approach has been considered for these types of tinnitus.

[2] Does "vascular conflict" means vascular compression of the facial nerve and auditory nerve? It is
convenient to include the picture of the neurovascular compression in patient of figs 2.

As reviewer commented, the mean of ‘vascular conflict’ in our manuscript indicates the neurovascular compression of cranial nerve (facial and/or cochlear nerve). We added the magnetic resonance images of the patient with tinnitus accompanied by right side hemifacial spasm as below;

![Magnetic Resonance Images](image)

[3] Clarify the tinnitus characteristics/type for each patient (see comments in Background).

We added the number of patients according to the tinnitus type at table 1.

[4] I found the data presented in paragraph 2 of this section and in fig 1 unclear. A table showing all measures for patients with and without tinnitus is missing (Table1?). Table 1 is also further cited in discussion: "MEG results of AEF...”

[5] Consider to show values of normal controls also.

AS recommendation of reviewer, we divided the table 1 into table 1, 2 and 3 with adding, and we added the MEG values of control side at the table 2 and 3.

MEG data as below;

**Table 2. Summary of Results (N100m latency)**

<table>
<thead>
<tr>
<th>Total</th>
<th>Clinical Factors</th>
<th>Auditory stimulation side</th>
<th>N100m latency (ms, mean ± S.D.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>HFS side</td>
<td>101.3 ± 14.3</td>
<td>0.198†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td>99.1 ± 10.0</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
<td>HFS side</td>
<td></td>
<td>92.8±7.9</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>--------------</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>97.0±7.1</td>
</tr>
<tr>
<td>no</td>
<td></td>
<td>HFS side</td>
<td></td>
<td>104.5±15.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>100.0±10.9</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>HFS side</td>
<td></td>
<td>98.5±9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>98.3±7.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>HFS side</td>
<td></td>
<td>102.0±15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>99.1±10.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≥50</td>
<td>HFS side</td>
<td></td>
<td>104.5±15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>100.0±10.9</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>HFS side</td>
<td></td>
<td>98.9±7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>97.0±7.1</td>
</tr>
<tr>
<td>Offender</td>
<td>AICA</td>
<td>HFS side</td>
<td></td>
<td>95.7±9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>97.3±7.8</td>
</tr>
<tr>
<td></td>
<td>PICA</td>
<td>HFS side</td>
<td></td>
<td>107.3±16.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control side</td>
<td></td>
<td>101.0±11.8</td>
</tr>
</tbody>
</table>

† N100m latency of HFS side vs. N100m latency of control side, paired t-test, paired t-test
‡ Comparison of N100m difference according to each factors, Mann-Whitney test
* Latency of N100m on the spasm side – latency of N100m on the normal side

Abbreviations: AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; S.D., standard deviation

### Table 3. Summary of Results (ECD strength)

<table>
<thead>
<tr>
<th>Total Clinical Factors</th>
<th>Auditory stimulation side</th>
<th>ECD strength (nAm, mean ± S.D.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>HFS side</td>
<td>27.5±9.4</td>
<td>0.265†</td>
</tr>
<tr>
<td></td>
<td>Control side</td>
<td>24.8±11.6</td>
<td></td>
</tr>
<tr>
<td>Tinnitus yes</td>
<td>HFS side</td>
<td>30.5±12.7</td>
<td>0.028†</td>
</tr>
<tr>
<td></td>
<td>Control side</td>
<td>18.8±5.1</td>
<td></td>
</tr>
<tr>
<td>Tinnitus no</td>
<td>HFS side</td>
<td>26.4±8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control side</td>
<td>27.1±12.6</td>
<td></td>
</tr>
<tr>
<td>Gender Male</td>
<td>HFS side</td>
<td>27.6±9.3</td>
<td>0.694‡</td>
</tr>
<tr>
<td></td>
<td>Control side</td>
<td>25.6±10.4</td>
<td></td>
</tr>
<tr>
<td>Gender Female</td>
<td>HFS side</td>
<td>27.5±10.2</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Control side</td>
<td>HFS side</td>
<td>Offender</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>≥50</td>
<td>24.6±12.1</td>
<td>30.31±1.0</td>
<td>26.5±10.5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>20.0±9.6</td>
<td>24.6±6.5</td>
<td>22.0±12.4</td>
</tr>
</tbody>
</table>

| Control side | 29.3±12.4 | 20.0±12.4 | 27.9±10.2 |

1 ECD strength of HFS side vs. ECD strength of control side, paired t-test, paired t-test

2 Comparison of the ratio of ECD strength according to each factors, Mann-Whitney test

* ECD strength of N100m on the spasm side / ECD strength of N100m on the normal side

Abbreviations: AICA, anterior inferior cerebellar artery; ECD, equivalent current dipole; PICA, posterior inferior cerebellar artery; S.D., standard deviation

[6] I found the whole discussion unclear. Authors must discuss studies on tinnitus using magnetoencephalography more than studies supporting the "central nervous system" origin of tinnitus. Unfortunately, lack of important data such as the type of patients' tinnitus, HFS treatment of each patient, follow-up including repeated MEG after treatment, do not permit to reach valid conclusions.

As reviewer pointed out, more data such as the treatment outcome of HFS, clinical follow-up data, and serial MEG data before/after treatment will give valuable information for better understanding and more firm evidence of pathophysiological mechanism. Unfortunately, we could not collect these data until now, and we also hope that we could obtain more information from further investigation.

[7] "Thus, we postulate that the pathophysiologic mechanism of tinnitus accompanied by HFS is different than that of tinnitus alone". This is obvious and needless.

We removed the sentence following reviewer’s comment.

Thank you again for your constructive comments and suggestions.

We hope you will find the revised manuscript suitable for publication in BMC Neurology.
Sincerely yours,

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