Reviewer's report

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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Reviewer: Steffen SR Rosahl

Reviewer's report:

The study contains original research material that definitely should be published. However, the manuscript needs to be greatly improved. Major compulsory revisions are necessary and I would like to see all the following points addressed before reviewing the manuscript a second time.

page 3 [Background]

[1]
“Contralateral tinnitus associated with hemifacial spasm (HFS) is not uncommon, and is seen in approximately 7% of patients with HFS.[1]”

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 Ruy et al. (1998).

[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.[2]”

if this conclusion is based on a single study (which reported improvement of tinnitus in 8 of the 10 patients studied.

Please refer to the original studies again, like this one:

Neurovascular decompression of the eighth cranial nerve in patients with hemifacial spasm and incidental tinnitus: an alternative way to study tinnitus.
Ryu H, Yamamoto S, Sugiyama K, Uemura K, Nozue M.
Abstract

OBJECT:
The authors sought to clarify the clinical characteristics of tinnitus resulting from neurovascular compression (NVC) of the eighth cranial nerve.

METHODS:
The authors explored the eighth cranial nerve in the cerebellopontine cistern during neurovascular decompression (NVD) of the facial nerve in 10 patients with hemifacial spasm who suffered from incidental tinnitus on the same side. The diagnosis of NVC of the eighth cranial nerve was confirmed in all patients. This condition was found in only seven of 114 patients with hemifacial spasm alone, indicating that NVC of the eighth cranial nerve is one of the causes of tinnitus (p < 0.001, chi-square test). The tinnitus resolved or was markedly improved after NVD of the eighth cranial nerve in eight patients (80%). Both pulsatile and continuous tinnitus responded well to NVD. All patients experienced various degrees of sensorineural hearing disturbance, but other neurotological examinations provided poor diagnostic value.

CONCLUSIONS:
It is the authors' opinion that sensorineural hearing loss and positive findings on magnetic resonance imaging are the most reliable evidence for the presence of tinnitus caused by NVC of the eighth cranial nerve.

[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:
please refer to the WORD file attached

page 6 [Results]

[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.
“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 pathophysiological 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.

“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?
“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.

[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.

If the authors still want to go ahead and publish the interesting MEG data they have obtained already, the focus of discussion should be on the fact, that not only there are a number of patients with HFS and tinnitus at the same time, but that it is also possible to find an objective correlate for their tinnitus in MEG da

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.