A prospective study on the role of the cerebellar (para)flocculus in tinnitus: the relation with electrophysiological parameters and inflammatory mediators

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Module 1Primary Objective: To objectify the relation between tinnitus and flocculus activity, quantified by direct response measurements on the flocculus. Tinnitus is quantified by the Tinnitus Functional Index score (TFI), tinnitus pitch and…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hearing disorders
Study type	Observational invasive

Summary

ID

NL-OMON55531

Source
ToetsingOnline

Brief title
The role of the flocculus in tinnitus

Condition

- Hearing disorders
- Nervous system neoplasms benign

Synonym
hearing of sound when no external sound is present, Tinnitus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Middels de Cock Hadders beurs

Intervention

Keyword: Cerebellum, Flocculus, Inflammation, Tinnitus

Outcome measures

Primary outcome

In module 1, we intend to objectify the relation between tinnitus, flocculus function and flocculus activity, quantified by direct response measurements on the flocculus.

In module 2, we intend to examine the relation between tinnitus and inflammation, quantified by expression of anti-glial fibrillary acidic protein (GFAP) as a marker of astrocytes, anti-CD11b (OX-42) as a marker for microglia like cells and cytokine levels in a choroid plexus biopsy, cytokine levels in serum and liquor and serum inflammation levels.

Secondary outcome

1. Relation between flocculus function and tinnitus presence and severity.

2. Relation between tinnitus and hearing thresholds

3. Relation between tinnitus severity and quality of life (EQ-5D)

Study description

Background summary

Tinnitus is the perception of sound without an external source. Chronic tinnitus is prevalent among 5-15% of the general population, in 20% of cases

negatively affecting quality of life. No good treatment strategies are available to this day, leading to a substantial economic burden to society. The pathophysiology of tinnitus remains obscure. The cerebellar flocculus recently received attention with regard to the pathophysiology of tinnitus in rats. In rats, once tinnitus is established, the paraflocculus presumably becomes an obligatory component in maintaining the condition.
In humans, the flocculus is located in the cerebellopontine angle (CPA). Chronic tinnitus is experienced by 61% of patients after CPA tumor removal. The flocculus is unavoidably manipulated during retrosigmoid removal of a CPA tumor. Manipulation of the flocculus or compression by the tumor might compromise the functions of the flocculus, leading to tinnitus. A retrospective study in humans after surgical CPA tumor removal showed a positive correlation between flocculus volume and tinnitus severity. Because the relation was present on both the ipsilateral and contralateral side, it suggests a relation between flocculus volume and tinnitus severity in general and therefore that the flocculus plays a role in the regulation of tinnitus.
It has been noted during cerebellopontine angle (CPA) surgery that the flocculus is sometimes firmly attached to the vestibulocochlear nerve. This might be due to inflammation, as a common pathophysiological mechanism in which two separate anatomical structures can glue together. Mean neutrophil-to-lymphocyte ratio was higher in patients with severe tinnitus than in controls and a correlation was present between serum levels TNF-α and tinnitus loudness, suggesting the presence of inflammation as well. By analyzing microglia activation and astrocyte presence in the choroid plexus and cytokine analysis, it could be possible to objectify inflammation in the CPA and particularly of the flocculus, which we hypothesize to lead to altered function and tinnitus.
To conclude, this project investigates several aspects of flocculus function, by determining tinnitus characteristics, by electrophysiological measurements with an electrode placed directly on the flocculus during surgery, and by exploring the possibility of inflammation.

Study objective

Module 1
Primary Objective:
To objectify the relation between tinnitus and flocculus activity, quantified by direct response measurements on the flocculus. Tinnitus is quantified by the Tinnitus Functional Index score (TFI), tinnitus pitch and tinnitus loudness.

Secondary objective(s):
1. Is there a relation between floccular activity and flocculus manipulation?

Module 2
Primary Objective:
To examine the relation between tinnitus and inflammation, quantified by expression of anti-glial fibrillary acidic protein (GFAP) as a marker of

astrocytes, anti-CD11b (OX-42) as a marker for microglia like cells and cytokine levels in a choroid plexus biopsy, cytokine levels in serum and liquor and serum inflammation levels.

Study design

This research protocol describes an observational study that will take place at the University Medical Center in Groningen at the department of Neurosurgery. Inclusion of patients is planned from February 17th, 2020 to September 30st, 2022, or until the target number of inclusions is acquired. Total follow-up is 6 weeks. Patients undergoing surgery for hemifacial spasms (microvascular decompression) or a CPA tumor (retrosigmoid removal) are eligible for this study. Patients who fulfill the inclusion and exclusion criteria and signed the informed consent will be included. This study consists of two modules. All patients will be asked to fill in a questionnaire regarding tinnitus and to undergo audiometry and vestibular tests the day before surgery. Six weeks after surgery patients will fill in the questionnaire again, which they receive at home. They can sent the questionnaire to the UMCG using an UMCG envelope.

Patients can choose in which module(s) they want to participate.
Both modules are pilot studies. In module 1, we intend to objectify the relation between tinnitus and flocculus activity, quantified by measuring direct response measurements on the flocculus during surgery. In module 2, we intend to examine the relation between tinnitus and inflammation, quantified by expression of anti-glial fibrillary acidic protein (GFAP) as a marker of astrocytes and anti-CD11b (OX-42) as a marker for microglia like cells in a choroid plexus biopsy, cytokine levels in serum and liquor and serum inflammation levels. A total of 20 patients with tinnitus and 20 patients without tinnitus is aimed to be included in module 1 and module 2.

Study burden and risks

There are no benefits for patients to participate in this study. Possible risks are minimal.
Vestibular test are obligatory measures for this study. Patients can become nauseous or dizzy, but there is no risk for their health.
In module 1 electrodes will be placed on the flocculus during surgery. Because of the chosen surgeries to take part in this module of the study, no additional manipulation or interventions are necessary to obtain access to the flocculus. The measurements on the flocculus itself are additional to standard patient care. The same measurements have been done before at the UMCG without complications (Kleinhuis et al., 2019).
In module 2 on the day of admission blood will be drawn, which is standard care. During surgery, after induction of anesthesia and before incision, one tube of blood will be drawn, using the arterial line if present. During surgery liquor will be aspirated, which is standard care. Liquor aspiration is not

performed for diagnostic or therapeutic purposes, but to optimize visualization during surgery by promoting brain relaxation. No additional procedures are needed to obtain liquor. Additional to standard care, a biopsy of the choroid plexus is taken during surgery. Because of the chosen surgeries to take part in this module of the study, no additional manipulation or interventions are necessary to obtain access to the flocculus. Taking a biopsy of the choroid plexus is a known and save diagnostic method used in clinical practice for diagnosis of suspected choroid plexus pathology for instance. Choroid plexus extirpation and coagulation also used to be the standard treatment for hydrocephalus. There is minimal risk of bleeding. This bleeding would be in plain sight so it can be easily coagulated. A biopsy of the choroid plexus will not be of influence on the homeostasis of the cerebrospinal fluid, because only approximately 1% of the choroid plexus will be biopsied.
Based on information above, we can conclude that this study is a low risk study (according to the NFU risk classification).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adult, aged 18 years or older;
- Undergoing microvascular decompression for hemifacial spasms or retrosigmoid removal of a CPA tumor.
- Agrees to participate in the obligatory measurements of this study
- Psychosocially, mentally, and physically able to fully comply with this protocol, including adhering to scheduled visits, treatment plan, filling out questionnaires and undergoing tests.
- Patient has sufficient mastery of the Dutch language to fill out the questionnaires.
- Signed and dated informed consent document prior to any study-related procedures

Exclusion criteria

- Suffering from bilateral CPA tumors
- Former surgery at the ipsi- or contralateral CPA region.
- Radiotherapy at the ipsi- or contralateral CPA region prior to surgery.
- Contralateral or bilateral complete deafness.
- Presence of pulsatile tinnitus synced with the heartbeat.

A potential subject who meets the following additional criterium will be excluded from participation in module 2 of this study:
- Presence of a (chronic) inflammatory disease.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-08-2020
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	20-05-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL68975.042.19
Other	NTR. Het identificatienummer is NL7646.