The role of the flocculus in tinnitus.

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26264

Source
Nationaal Trial Register

Brief title
-

Health condition

Tinnitus

Sponsors and support

Primary sponsor: University Medical Center Groningen
Source(s) of monetary or material Support: Direct

Intervention

Outcome measures

Primary outcome

Part 1: To evaluate the influence of surgical flocculus manipulation and presence of a CPA tumor on flocculus function and its relation with tinnitus presence and severity. Flocculus function is objectified by flocculus volume on a MRI and vestibular and eye movement tests. Tinnitus severity is quantified by the Tinnitus Functional Index score (TFI), tinnitus pitch and tinnitus loudness.

Part 2: To objectify the relation between tinnitus and flocculus activity, quantified by direct

response measurements on the flocculus.

Part 3: 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 and serum inflammation levels.

Secondary outcome

Part 1:
1. Relation between flocculus function and tinnitus presence and severity.
2. Relation between CPA tumor volume and tinnitus
3. Relation between flocculus volume and fossa posterior volume
4. Differences in flocculus function before and after treatment
5. Differences in tinnitus severity before and after treatment
6. Related between tinnitus and hearing thresholds?
7. Relation between tinnitus severity and quality of life (EQ-5D)

Part 2:
1. Relation between floccular activity and flocculus function before flocculus manipulation

Study description

Background summary

Rationale: 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 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 determines the influence of flocculus manipulation and CPA tumor presence on the prevalence of tinnitus. Moreover, it investigates several aspects of flocculus structure and function, by determining tinnitus characteristics and flocculus morphology, by electrophysiological measurements with an electrode placed directly on the flocculus during surgery, and by exploring the possibility of inflammation.
Objective: The study is subdivided in 3 parts. In part 1, we intend to explore the influence of surgical flocculus manipulation and presence of a CPA tumor on flocculus function and its relation with tinnitus presence and severity. Flocculus function is objectified by flocculus volume on a MRI and vestibular and eye movement tests. Tinnitus severity is quantified by the Tinnitus Functional Index (TFI) questionnaire and tinnitus pitch and loudness. In part 2, we intend to objectify the relation between tinnitus and flocculus activity, quantified by direct response measurements on the flocculus. In part 3, 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 and serum inflammation levels.
Study design: This is an observational study.
Study population: The study population consists of patients undergoing treatment for either a CPA tumor (radiotherapy or translabyrinthine/retrosigmoid surgery), or microvascular decompression CPA-surgery (for hemifacial spasms or trigeminal neuralgia). All patients are 18 years or older and do not suffer from bilateral pathology.
Main study parameters/endpoints: The main study parameters of part 1 are treatment group, flocculus volume on a MRI, vestibular and eye movement tests, Tinnitus Functional Index score, tinnitus pitch and tinnitus loudness. In part 2 the main study parameter is direct response measurements on the flocculus. In part 3 the main study parameters are the expression of anti-glial fibrillary acidic protein (GFAP) as a marker of astrocytes, anti-CD11b (OX-42) as a marker for microglia like cells in a choroid plexus biopsy and serum inflammation levels.

Study objective

Manipulation of the flocculus and presence of a cerebellopontine angle tumor comprises the functions of the flocculus, leading to tinnitus. Moreover, inflammation in the cerebellopontine angle and particularly of the flocculus leads to altered function and thus tinnitus.

Study design

Time point 1: approximately 6 weeks before treatment
- Patients are asked to fill out a questionnaire, containing questions about tinnitus presence and characteristics, the Tinnitus Functional Index and the EQ-5D quality of life questionnaire (appendix: F1. Vragenlijst).
- Standard tone audiometry and speech audiometry
- Tinnitus pitch and loudness matching

- Vestibular and eye movement tests
- High resolution MRI-scan for determining flocculus volume and tumor volume if present, by using iPlan 3.0 software (BrainLab AG, Munich, Germany) as in Mennink et al.(2018). If patients are referred from another hospital, MRI scans are already available. If these scans are made more than one year ago or the quality is not sufficient, new scans will be made at the UMCG.

Time point 2: surgery (only patients participating in part 2 and/or part 3
Part 2: During surgery, electrophysiological response of the flocculus on sound stimuli are measured with an electrode on the flocculus before the flocculus is manipulated. In addition, the operating neurosurgeon will objectify the flocculus morphology
Part 3: The day before surgery, a blood sample will be taken to measure mean platelet volume, platelet distribution width, platelet count, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio. This blood sample is standard care. During surgery, additionally a biopsy of the choroid plexus is taken, which is used to perform immunohistochemistry to objectify inflammation.

Time point 3: approximately 6 weeks after treatment
- Patients are asked to fill out a questionnaire, containing questions about tinnitus presence and characteristics, the Tinnitus Functional Index and the EQ-5D quality of life questionnaire (appendix: F1. Vragenlijst).
- Standard tone audiometry and speech audiometry
- Tinnitus pitch and loudness matching
- Vestibular and eye movement tests
- High resolution MRI-scan for determining flocculus volume and tumor volume if present, by using iPlan 3.0 software (BrainLab AG, Munich, Germany) as in Mennink et al.(2018). If patients are referred from another hospital, MRI scans are already available. If these scans are made more than one year ago or the quality is not sufficient, new scans will be made at the UMCG.

Intervention

N/A

Contacts

Public
Universitair Medisch Centrum Groningen
Lilian Mennink

050 361 28 37
Scientific
Universitair Medisch Centrum Groningen
Lilian Mennink

050 361 28 37

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Adult, aged 18 years or older;
- Undergoing microvascular decompression for hemifacial spasms or trigeminal neuralgia or treatment of a CPA tumor (translabyrinthine/retrosigmoid surgical removal or radiotherapy);
- Agree to participate in part 1 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

Patients meeting the following criterium will be asked to participate in part 2 and/or part 3 as well:
- Undergoing retrosigmoid CPA tumor removal or the microvascular decompression for hemifacial spasms

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Suffering from bilateral CPA pathology (i.e. tumor or neurovascular conflict)
- Bilateral complete deafness.
- Presence of contra-indications for a MRI-scan.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)

Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2019
Enrollment:	100
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N/A

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL7646
Other	METC UMCG : METc 2019/133

Study results

Summary results
N/A