Are elevated prolactin levels harmful for the retinal and sublingual microvascular bed?

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Primary objective: To evaluate whether patients with a prolactinoma have signs of altered vascular function and/or morphology in the retina or sublingual tissues in comparison to healthy controls. Secondary Objectives: 1. To evaluate whether there...

Ethical review	Approved WMO
Status	Pending
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON32787

Source
ToetsingOnline

Brief title
Prolactin and the retinal and sublingual microvascular bed.

Condition

- Hypothalamus and pituitary gland disorders
- Retina, choroid and vitreous haemorrhages and vascular disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
benign pituitary tumor, pituitary adenoma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Microvascular, Prolactin, Retina

Outcome measures

Primary outcome

Main study parameter/endpoint

The extent of altered vascular function or morphology in the retina and sublingual tissues in comparison to healthy controls.

Secondary outcome

Secondary study parameters/endpoints

1. The difference in inflammatory markers, a vessel wall marker, procoagulant markers, markers of insulin resistance and lipids in patients with a prolactinoma, in comparison to healthy controls.

2. The difference in albuminuria in patients with a prolactinoma in comparison to healthy controls.

3. The extent of tube formation after patient*s plasma is incubated in the in vitro angiogenesis assay, compared to the extent of tube formation upon incubation with plasma from healthy controls.

4. The serum level of 16 kDa prolactin fragments in patients with prolactinoma, in comparison to serum levels in healthy controls.

Study description

Background summary

Besides being a classical pituitary hormone, recent observations indicate that prolactin could have several other functions as well. In illustration, prolactin may have a pro-coagulant effect. Additionally prolactin has been shown to modulate the immune function. Furthermore it may play a role in new vessel formation through its effect on the vascular endothelium. Full-length prolactin stimulates angiogenesis in vivo and in vitro, whereas 16 kDa N-terminal prolactin fragments suppress this process.
Imaging of the retina and sublingual tissue provides insight in the status of the vascular endothelium and can highlight the different phases of angiogenesis. There are several techniques to easily show the vasculature in the retina and the sublingual vasculature.
Of interest, elevated persistent prolactin levels are permitted in older patients with a prolactinoma. In case this study shows that prolactin stimulates angiogenesis in the retina and in the sublingual tissues, it is likely that angiogenic processes elsewhere in the body are also stimulated by prolactin. This would imply that for patients who have comorbidities in which angiogenesis plays a role, a high prolactin level is extra unfavourable.
When this study will indicate that prolactin stimulates vessel formation, we plea for a study in which the effect of prolactin lowering on angiogenesis in patients with a prolactinoma will be investigated. This would in particular be interesting for older patients who have co-morbidity in which angiogenesis plays a role in the pathology, whose prolactin levels are currently not agressively lowered.
When this study shows that prolactin stimulates new vessel formation, it could also be interesting to study whether patients without prolactinoma and co-morbidity in which angiogenesis plays a role, would profit from prolactin lowering therapy. In healthy patients without a prolactinoma there is such a variation in physiological prolactin levels, that it can be worthwile to lower prolactin.

Study objective

Primary objective: To evaluate whether patients with a prolactinoma have signs of altered vascular function and/or morphology in the retina or sublingual tissues in comparison to healthy controls.

Secondary Objectives:
1. To evaluate whether there is a difference in plasma in inflammatory markers, in coagulation factors, in markers of insulin resistance and in lipids between patients with a prolactinoma and healthy controls.
2. To evaluate whether patients with a prolactinoma have more albuminuria in comparison to healthy controls.
3. To evaluate the extent of tube formation after a patient*s plasma is incubated in the in vitro angiogenesis assay, compared to the extent of tube formation upon incubation with plasma from healthy controls.
4. To evaluate whether levels of 16 kDa prolactin fragments in patients with a

prolactinoma are different from levels in healthy controls.

Study design

Patients visiting the outpatient clinic from the department of Endocrinology or Internal Medicine with an active prolactinoma will be included in this case-control study. They should enter and finish the study before start of prolactin lowering medication. Patients will be asked to bring a person who will serve as control.
The research physician will perform an anamnesis and physical examination. Blood will be withdrawn and SDF is done. Furtehrmore, patients and controls are asked to collect their urine for 24 hours in order to assess the extent of micro-albuminuria.
A second visit to the AMC is planned for fluoresceine angiography and OCT.

Blood withdrawal
At the first visit blood was withdrawn (40 ml). Factors that play a role in angiogenesis, inflammation, coagulation and insulin resistance and colesterol will be studied.

In vitro angiogenesis assay
Endothelial cells will be resuspended in growth medium with patient*s or control*s plasma, with or without prolactin receptor antagonist. After 16 hours, the extent of endothelial tube formation will be quantified.

Sidestream Dark Field (SDF)
Investigators will use SDF imaging to analyze functional changes in the sublingual microcirculation. Five consecutive videoclips will be made of different sites of the sublingual microcirculation. Video clips will be analyzed blindly and randomly by a resident ophthalmology, using different approaches, namely a validated semi-quantitative score of bloodflow, and a quantitative score of vascular capillary density and vessel diameter.

Fluorescein angiography (FAG)
Fluorescein angiography will be conducted in conjunction with colour fundus photography at baseline. Investigators will use digital fluorescein angiograms to determine presence or absence of retinal vascular abnormalities. The following angiographic and photographic procedures are to be followed. After pupil dilation with tropicamide 1% and prior to fluorescein dye injection, 35 degree red-free and colour photographs will be taken of the maculae of one eye. Next, 5 ml of fluorescein 10% dye will be injected IV into the antecubital vein. Photographs of the study eye will be taken during the early transit phase from 15 to 45 seconds, at 60 to 90 seconds, and at 5 and 10 minutes after completion of the fluorescein dye injection. Photographs that are taken of the macula of the study eye during the fluorescein transit will typically include 1 stereoscopic pair at 3-5 minutes. Photographs of the macula of the fellow eye will be taken at 2 and 10 minutes after fluorescein dye injection. Photographs

will be analyzed afterwards by two blinded ophthalmologists.

Optical coherence tomography (OCT)
An OCT scan will be made of the macular region of the retina of the research eye. It will give clues about retinal thickness and vascular leakage of retinal capillaries. In conduction with FAG, the OCT scan will be made. This will take 5 minutes. The images will be analyzed afterwards.

Collection of urine
Patients will be asked to collect urine for 24 hours, in order to assess the extent of microalbuminuria. Normally not much protein is filtererd by the kidney. However, in case of renal damage proteins will be filtered more easily.

Participation of healthy controles.
Patients will be asked to bring someone they know iwho s willing to to serve as a control. In case that patients will not be able to find someone who can serve as control, we will find those patients through advertisement (please check appendix for advertisement).

Study burden and risks

No additional harm is expected due to sublingual and retinal evaluation (SDF, OCT and fluorescein angiography). These methods are routinely performed and part of several prior study protocols in the Academic Medical Centre, Amsterdam (department of Ophthalmology). Patients should stay fasted for the first study visit to the AMC until blood is withdrawn, and should not take any drinks containing caffein until SDF is done.
As mentioned in the Introduction section, additional knowledge is needed in order to evaluate the biological action of elevated prolactin levels on angiogenesis-related pathology, in order to assess the long term effects of persistent increased prolactin levels that are currently permitted after middle age (in both male and female patients with prolactinoma).

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

(For both patients as controls, with obviously exception of the first inclusion criteria)
Patients (both women and men) with active prolactinoma (either micro- or macroprolactinoma, with prolactin levels above >50 ng/ml
Age 20-60 years.
Written informed consent

Exclusion criteria

(For both patients as controls)
Macroprolactinemie.
Infundibulum infiltration.
Diabetes mellitus type 2.
Pregnant women.
Premature atherosclerosis.
Use of antidepressive and antipsychotic medication.
Presence of co-morbidity that could affect retinal vasculature or its matrix.
History of hypersensitivity or allergy to fluorescein.
Inability to obtain SDF, fluorescein angiograms or OCT*s of sufficient quality to be analyzed and graded.
Active malignancy.
Systemic disease with a life expectancy shorter than the duration of the study.
Inability to adhere to the protocol with regard to injection and visits.
Legally incompetent adult.

Refusal to give written informed consent.
Additional use of medication that could affect neo-angiogenesis.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2009
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL29861.018.09