A multicenter prospective study of biochemical profiles of monoamine-producing tumors: utility for diagnosis and determinants of clinical presentation. (The PMT study)

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Primary objective:to identify new and improved disease biomarkers and establish the biochemical and molecular basis for variations in the clinical presentation of the different groups of tumors.Secondary objectives:• compare the diagnostic utility…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON36293

Source
ToetsingOnline

Brief title
The PMT study: Prospective Monoamine-producing Tumor study

Condition

- Other condition
- Adrenal gland disorders

Synonym
pheochromocytoma ; catecholamine producing tumor

Health condition

hypertensie

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: catecholamines, metanephrines, paraganglioma, pheochromocytoma

Outcome measures

Primary outcome

• Numbers of true-positive, false-positive, true-negative and false-negative

results of each biochemical test.

• Biochemical, metabolic, molecular and secretory profiles as related to the

clinical manifestations, malignant development and germline mutations.

• Blood pressure profiles, cardiac function parameters and indices of disease

progression.

Secondary outcome

na

Study description

Background summary

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that derive from adrenomedullary tissue (pheochromocytomas) in about 85% of cases and from extra-adrenal chromaffin tissue (paragangliomas) in 15% of cases. PPGL*s represent a surgically correctable cause of hypertension, a result of their capacity to secrete catecholamines. As a consequence of the unpredictable, often explosive nature of this secretion, the tumors are potentially lethal if not quickly diagnosed and treated. Fortunately, once suspected, appropriate biochemical testing now makes it unlikely that the

presence of a catecholamine-producing tumor will be missed. In particular, recognition that the O-methylated metabolites of catecholamines - the metanephrines - are produced continuously within chromaffin tumor cells and independently of variations in secretory activity has led to promulgation of these analytes as superior for diagnosis of PPGLs compared to other analytes.
PPGL*s occur either sporadically or as a part of several hereditary syndromes: MEN2), VHL, NF 1, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127.
The clinical presentation and manifestations of PPGL*s are highly variable and only now becoming understood to be influenced by the underlying mutation. There is currently no method to predict malignant potential or even diagnose the presence of malignant disease from immunopathological examination of a resected tumor. This diagnosis continues to depend on identification of metastases, at which stage the response to available therapies is limited.
Based on this extensive knowledge on the pathophysiology, diagnosis and treatment of PPGLs tumors, implementation of innovative approaches aimed at increasing the positive and negative predictive value of early stage diagnostics as well as post-therapeutic monitoring is appealing. One of those approaches is the so-called *miRNA-profiling*. MiRNA-profiling relies on the detection and monitoring in body fluids of non-coding RNAs, the so-called micro-RNAs (miRNA). Since the discovery of RNA interference, miRNAs have been recognized as regulators in numerous developmental and physiological processes. MiRNAs have been linked to cancer development and progression as well as other diseases such as diabetes and amyotrophic lateral sclerosis (44). A mammalian miRNA expression atlas based on small RNA library sequencing has been published by the NIH. Interestingly, it has been shown that HIF may be involved in up-regulation of miR-210 and miR-373, possibly implicated in DNA repair pathways. Recently, miRNAs in serum and blood are emerging as a new and promising class of biomarkers for the diagnosis of cancer and other diseases.
In this context, a further aim of this project would be to characterize additional miRNA-biomarkers for PGGL through comparison in a prospective setting of the miRNA-profiles detected in serum and urine of the patients with the clinical patterns of disease and the biochemical profiles of the tumors. Moreovoer, miRNAs could also represent future therapeutic targets.

Study objective

Primary objective:
to identify new and improved disease biomarkers and establish the biochemical and molecular basis for variations in the clinical presentation of the different groups of tumors.

Secondary objectives:
• compare the diagnostic utility of urinary and plasma free metanephrines and establish an effective strategy for distinguishing true- from false-positive test results in patients with suspected PPGL.
• to establish relationships between biochemical and metabolic profiles, underlying genotypes and presentation of disease.

• to compare miRNA-profiles in patients with suspected PPGLs with healthy individual controls

Study design

This is mainly a prospective observational study with no specific extra interventions for all patients suspected to have a PPGL. Alle diagnostic methods are already used in regular patient care. The extra measurements include a blood sample for miRNA profiles in all suspected patients and an overnight urine sample for measurement of urinary free metanephrines in those patients in whom a PPGL is possible (equivocal test results) or in whom it is confirmed.

All patients with suspected PPGLs will follow several diagnostic and follow-up phases as outlined in the protocol. The first 3 phases are scheduled within the first 3 years of the study while the last phase will be carried out over the entire 5-year period. Since these patients will be seen in regular care, there is no fixed date schedule.
Phase 1: patients enter the study for diagnostic testing.
Phase 2: involves follow-up testing for confirmation of the biochemical diagnosis of pheochromocytoma in a subset of patients with equivocal test results.
Phase 3: involves disease characterisation (only patients with biochemically confirmed PPGL).
Phase 4: involves disease verification and patient follow-up.

In all hypertensive and normotensive subjects, only blood and urine sampling will be carried out for establishing reference intervals for biochemical tests.

The study will last for five years but all patients will be enrolled in the first three years of the study. Follow-up will take place over minimum of two and a maximal five years.
• start date: 1-10-2011
• end date: 1-10-2016

Study burden and risks

There are no extra risks involved since there are no extra interventional or diagnostic procedures. This also applies for venous blood sampling or urine sampling since this should done anyway.

In the normotensives there is a small risk of bruising when venous blood sampling is done.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Male and female patients (all ages, including children above 5 yr) with suspected pheochromocytoma/paraganglioma if they fulfill one or more of the are following criteria:
(i) patients with a previous history of PPGLs.
(ii) new onset of hypertension or therapy-resistant hypertension or hypertensive episodes and/or symptoms suggestive of PPGLs.
(iii) family history of PPGL or genetic mutations known to predispose individuals to develop PPGLs.
(iv) presence of an accidently found adrenal tumor
(v) any other reasonable clinical suspicion of a PPGL ;For establishing reference intervals the

following patients will be enrolled:
(i) treated or untreated male and female patients with primary hypertension (>140/90 mm Hg) (above 18 yr).
(ii) healthy normotensive volunteers (above 18 yr)

Exclusion criteria

• Patients with impaired mental capacity that precludes informed consent.
• Subjects who need medications that may interfere with or invalidate outcome parameters (e.g., tricyclic antidepressants).
• Pregnancy does not constitute criteria for exclusion from the protocol. However, in pregnant women no PET scanning, MIBG scanning or contrast CT will be performed.
• Patients at risk from injury from the MRI magnet due to implantable metal or who suffer from anxiety in enclosed spaces are excluded from MRI.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2013
Enrollment:	800
Type:	Actual

Ethics review

Approved WMO

Date:	07-02-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL33816.091.11