cognitive dysfunction and neuroimaging in testicular and breast cancer survivors

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON34365

Source
ToetsingOnline

Brief title
CONNECT;Cognition and the neural network: effects of chemotherapy

Condition

- Cognitive and attention disorders and disturbances

Synonym
cognitive deficits, memory and concentration problems

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: (f)MRI, Chemotherapy, Cognition

Outcome measures

Primary outcome

MRI scanning will be performed using a Philips Intera 3.0 Tesla scanner with an eight channel Sense head coil. MRI imaging parameters:

1. 3-dimensional T1-weigthed sequences followed by (automated) volumetric measurement, as a gross measure for tissue loss.
2. FLAIR sequence to determine presence and extent of demyelination.
3. MR spectroscopy allows the safe in vivo measurement of brain neurochemistry. Compounds that can be identified are N-acetylaspartaat (NAA), choline (Cho) en myo-inositol (MI). NAA is contained almost exclusively within neurons and is considered a neuronal marker for neuronal density and viability. Cho indicates integrity of neuronal structure. MI reflects glial content.
4. Diffusion Tensor Imaging (DTI) will be used to study the (density) of fibers subserving well-defined functional networks and as such provide an index of damage in the normal appearing white matter. The outcome measures will be used to study correlations with specific functional deficits.
5. Functional MRI: EPI sequence, 38 slices/2,5 mm, 0,5 mm slice gap, TR = 2.1 s, axial sequence acquisition. We will use the following, well-studied paradigms measuring executive functioning and memory to investigate changes in the blood oxygen level dependent (BOLD) response, reflecting neural activity.

Tower of London task: a task widely used to investigate executive/planning processes and known to robustly activate the dorsolateral prefrontal cortex.

Flanker task: previous studies by our group consistently show impaired performance on this task by patients treated with chemotherapy. It provides a means for examining interference control processes. Activation of the anterior cingulate cortex (a central component of the neural circuit for action monitoring) is reliably observed during this task.

Paired associates task: a task concerning implicit memory. The medial temporal lobe (e.g. hippocampus) is reliably activated during encoding as well as retrieval of stimuli.

Resting state: subjects will be instructed to lie still, while no specific cognitive task is presented. These so-called resting state data contain information about several well-known brain networks, as well as the default mode network, which is thought to reflect baseline activity of the brain. Heart rate and respiration will be recorded during this scan and will be used as regressors in our analyses, to take into account the effect that speed of respiration and heart rate has on signal changes in BOLD response.

Secondary outcome

In addition to the tests that are administrated while MRI scans are being acquired, the patients will also be tested with a neuropsychological examination. The neuropsychological tests will take place before the MRI

scanning session.The neuropsychological examination will consist of the following classical neuropsychological tests, which were also included in previous neuropsychological examinations conducted at the NKI-AvL: Hopkins Verbal Learning Test, Trail Making Test, Verbal Fluency Test, Digit Symbol Test, Wechsler Memory Scale, Fepsy Finger Tapping, Flanker task, Behavioural Assessment of the Dysexecutive Syndrome - zoo-map, Digit span, Visual Reaction time task. These tests are included to obtain information on the current cognitive status of the participants.

The following data will be collected for all participants: Age, educational status, smoking habits, alcohol intake, body mass index, age at menopause (if applicable) and type of menopause (natural or artificial), previous use of hormone replacement therapy, psychological distress (Hopkins Symptom Checklist), current mood state (Profile Of Mood States), health related quality of life (EORTC QLQ-C30), self-reported cognitive problems (MOS questionnaire), self-reported stress (Perceived Stress Scale), presence of Post Traumatic Stress Disorder (PTSD) (Trauma Questionnaire), lifetime depression and PTSD (Compositie International Diagnostic Interview (CIDI)) , self-reported personality traits (TIPI), self-reported medical history and medication use.
For the women and men that underwent chemotherapy the following additional information will be obtained through the medical records: kind of cytotoxic treatment, radiotherapy yes/no, endocrine therapy yes/no (if applicable). For the breast cancer and testicular cancer patients that did not undergo chemotherapy, the following information will be obtained through the medical

records: radiotherapy yes/no, endocrine therapy yes/no (if applicable).

To study possible mediating effects of stress on the relation between chemotherapy and cognition, cortisol levels will be measured in hair samples. Through this method, cortisol levels can be measured for a period up to the past six months. Earlier research suggested a dysregulation in hypothalamic-pituitary-adrenal (HPA) axis responsiveness among breast cancer survivors.

Recent studies have indicated a possible mediating role for specific genetic polymorphisms, e.g. APOE, BDNF and COMT, in the development of cognitive dysfunction following chemotherapy. Therefore, saliva samples will be taken to screen for these genetic polymorphisms in relation to cognitive outcomes after cancer treatment. Blood samples will be collected in all subjects to analyze cytokine levels, e.g. IL1, IL6 and TNFα. In cancer patients, cytokines have been shown to be increased. The deregulation of cytokines has been associated with neurotoxicity and deficits in cognitive performance following chemotherapy . Blood samples will also be used to assess hormonal levels in the testicular cancer patients. In males, lower endogenous testosterone-levels may be related to cognitive dysfunction. It has been shown that chemotherapy in males may lead to a greater risk of low testosterone levels.

Study description

Background summary

Over the last years, interest in cognitive deficits after chemotherapy has increased. In several neuropsychological studies in breast cancer patients we as well as others have found cognitive impairments after chemotherapy. In a series of neurophysiological studies we also found abnormalities in EEG measures in this patient population. A recent study by our group showed converging evidence for neurocognitive problems based on neuropsychological and neurophysiological measures and self-report of cognitive complaints up to five years after cessation of treatment with chemotherapeutic treatments. In addition, our animal studies have demonstrated long-lasting dose-dependent decreases in cell proliferation in the hippocampal formation in rats, after single intravenous administration of methotrexate and other cytostatics. Despite these indications of long-lasting effects on the central nervous system, resulting in persistent cognitive impairment, our understanding of the nature and the mechanism(s) driving this compromise is fragmentary at best.

Study objective

In our recent studies we found indications of the existence of particular cognitive deficits as well as memory impairments following different regiments of cytostatic agents. Together with the indications form our animal studies of a potential contributory role of reduced neurogenesis in the hippocampus and the promising results of our pilot data, compelling arguments are provided to initiate a study aiming to:

- Investigate the late effects of chemotherapy on neuropsychological performance, and MRI brain function and structure in patients that received standard-dose chemotherapy for breast cancer or testicular cancer compared to disease specific and healthy controls.

In breast cancer survivors, there will be also investigated whether there are difference in cognitive impairment between high-dose (from a pilot study from our group (PTC07.0766)and low-dose chemotherapy. By including testicular cancer survivors, we can investigate whether memory impairments also occur following different regiments of cytostatic agents.

Study design

This crossectional study is a collaboration between the department of Psychosocial Research and Epidemiology and the department of neuro-oncology of the NKI-AvL and the department of Radiology of the Academic Medical Center.In this study, patients from the NKI-AvL, VU medical center (VUmc), Daniel den Hoed Kliniek and Leids University Medical Center (LUMC) will be included.

Study burden and risks

Participants will be tested once. The test assessment will last three hours and consists of a semi-structured interview, several questionnaires, several neuropsychological tests, and an MRI scanning session of one hour. Half of the scanning time, the patient is actively engaged in task performance. The other half of the time, MR sequences are acquired for which no active involvement of the patient is required.
During the MRI scans, the patient has to lie still in the scanner which is sometimes considered inconvenient. Moreover, the scanner produces noise, which is effectively reduced by the use of earplugs and headphones. When standard safety rules are applied (e.g., no ferromagnetic objects inside the scanner room) no risks exist for the patient. Ample experience with patient populations have indicated that this procedure is feasible and is not considered too burdensome. Feasibility of this assessment was also demonstrated in a pilot study (PTC07.0766)2 by our group, where all participants finished all measurements. This study is similar to this pilot study except for the inclusion of testicular cancer patients. Furthermore, a prospective study in breast cancer patients of our group has recently been approved (PTC10.1229), which method is also highly similar to this study.

During assessment, a small sample of hair will be collected to allow analysis of cortisol levels (see attached file with instructions about hair sampling). We interviewed a random sample of patients visiting the chemotherapy day-care unit. Patients indicated not to have any specific concerns regarding this measure. Blood will be collected to allow for analyses of hormonal levels as well as cytokines which may play a mediating role in neurotoxic effects of chemotherapy. In addition, saliva samples will be taken to allow for genetic screening for factors related to cognitive functioning. Oral collection of saliva is a non-invasive and easy way to collect specimen for genetic analysis. Finally, some blood will be taken by an experienced and certified investigator, which should not be burdensome.

No information regarding individual test performance, MRI findings (except for incidental findings) and findings on individual cortisol measures will be communicated to participants. The assessments will take place at the Academic Medical Center of the University of Amsterdam (AMC), because of functional MRI facilities at that site. Travel expenses and parking costs will be reimbursed. To allow for a short break during the assessment, patients will be given a lunch voucher.

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

All groups:
- sufficient proficiency in the Dutch language
- age under 70 years (to allow use of the same neuropsychological test battery)
- eligibility to undergo the MRI scanning session;Cross sectional part, experimental group:
- previous participation in our neuropsychological study
- having been treated with standard-dose chemotherapy (FEC) ;Cross-sectional part, control group
- previous participation in our neuropsychological study
- No treatment with chemotherapy ;Control group:
- Healthy subjects need to be matched for age

Exclusion criteria

- metastatic disease or relapse since previous neuropsychological examination
-history of neurological or psychiatric signs that can impact cognitive functioning
- alcohol or drug abuse

- conditions that preclude MRI examination

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-03-2011
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	13-01-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	NL33374.031.10