The NeuroFab Study: Two year follow-up of Cognitive and Psychological functioning in patients with Fabry Disease.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON43300

Source
ToetsingOnline

Brief title
The NeuroFab Study

Condition

- Metabolic and nutritional disorders congenital
- Structural brain disorders
- Cognitive and attention disorders and disturbances

Synonym
alpha-galactosidase A deficiency, Anderson-Fabry disease, Fabry Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cognition, Fabry Disease, Neurological manifestations, Neuropsychological tests

Outcome measures

Primary outcome

Primary objective:

* Cognitive functioning and prevalence of cognitive and psychological

impairment in Fabry patients assessed with a neuropsychological test battery

Secondary outcome

Secondary objectives:

* Changes in cognitive and psychological functioning and prevalence of

cognitive impairment in Fabry patients assessed with a neuropsychological test

battery during two years follow-up

* Prevalence of depression assessed with The Center for Epidemiologic Studies

Depression Scale Revised

* Sleep quality and sleep habits assessed with the Pittsburgh Sleep Quality

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* Physical activity assessed with the International Physical Activity

Questionnaire *last seven days*

* Coping strategies assessed with the Utrecht Coping List

Study description

Background summary

Fabry Disease (FD) is a rare, progressive, X-linked metabolic disorder, that belongs to the group of lysosomal storage diseases. GLA gene abnormalities cause absence or deficiency of lysosomal *-galactosidase A (*-GalA) leading to accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3). Progressive accumulation of Gb3 is prominent in vascular endothelium, brain, kidneys and heart. FD has a wide range of symptoms and is usually divided into the classic phenotype, most often seen in male patients without residual enzyme activity, and the non-classical phenotype. In untreated FD renal disease, cardiac events and transient ischaemic attacks (TIA) or cerebrovascular accidents (CVA) occur frequently. In contrast, patients with non-classical FD usually have a less progressive disease course and symptoms may be restricted to one organ.

Since 2001 enzyme replacement therapy (ERT) is available for patients with FD. Studies on the long therm effect of ERT have shown that ERT can postpone complications on heart and kidneys and might improve quality of life (QoL), gastrointestinal symptoms and pain, primarily when started in the early course of FD.

Cerebral involvement is common in patients with FD. The prevalence of white matter lesions (WMLs) increases with age and is present in all patients above 54 years of age. The prevalence of often premature CVA/TIA is up to 24% in males with classic phenotype, while the two largest Fabry registries report a prevalence of 6.9%-25% in male patients and 4.3%-21% in female patients.

The effect of ERT on cerebrovascular manifestation of FD is unclear. Evidence shows mixed results. Some studies showed halt or reverse of WMLs, while other studies demonstrated progression of WMLs and occurrence of stroke and/or TIAs during ERT in Fabry patients.
Research in non-Fabry populations shows that dysfunction of cerebral blood flow, microvascular brain damage and WMLs increase the risk of cognitive impairment and dementia. These abnormalities are all present in FD. In addition, it has become clear from personal clinical experience that some males with end stage classical FD may develop severe cognitive impairment. Indeed, the results of a systematic review suggested an association between FD and cognitive impairment (executive functioning, information processing speed and attention). However, definite conclusions could not be drawn due to the limited amount of available evidence.

This review also summarized the available evidence on the prevalence of depression in FD and discussed their relationship. The largest included study reported a depression prevalence of 46% of which a significant part was

undiagnosed. It is still under debate whether depression is a result of difficulties in coping with symptoms of FD, especially chronic pain, or a result of cerebrovascular disease. It is important to realize that depression or depressive symptoms may impair performance on neuropsychological tests. Several studies on neuropsychological functioning have been carried out since the abovementioned systematic review, and these showed variable outcomes. Altogether, the extent of cognitive impairment in FD remains unclear.

Study objective

Previous studies have suggested an association between FD and cognitive impairment but these were flawed either by lack of power, used variable assessment of cognitive functioning and/or merged results of different phenotypes and sexes. It is of great importance to gain more insight into the debilitating cognitive problems in FD and the occurrence of psychological distress and its influence on cognitive functioning.

In summary, FD is a severe and debilitating disease which affects cognitive and psychological functioning, with unclear effect of ERT. We hypothesize that Fabry patients have decreased cognitive functioning measured by standardized neuropsychological instruments, compared to Dutch normative data, which is attributable to cerebrovascular manifestations of FD. These cognitive complications are probably most prominent in males with classical FD.

Study design

The Academic Medical Centre (AMC) in Amsterdam is the only referral center for Fabry patients in the Netherlands. Fabry patients are frequently monitored, with intervals ranging from once every three months immediately after start of ERT to once every four years in asymptomatic female patients. During follow-up visits Fabry patients undergo routine clinical care including MRI-brain, testing and follow-up of biomarkers and physical examination. All Fabry patients have been asked for informed consent to use their clinical data for research. These data have been prospectively entered into a clinical database which will be used in our study.
In this prospective cohort study, data on cognitive and psychological functioning will be gathered using standardized neuropsychological tests and questionnaires. These tests and questionnaires are not included in the routine clinical care for Fabry patients. For all neuropsychological tests and most of the questionnaires extensive Dutch normative data are available. These data are adjusted for age, gender and education. All Fabry patients known in this center will be screened by telephone for eligibility, according to inclusion and exclusion criteria. Included patients will be followed for two years after inclusion. Excluded patients and patients unwilling to participate will be compared to included patients for possible differences in demographic and disease characteristics, collected through our clinical database. In the two

years follow up period the included patients will be evaluated three times. There will be three visits to the AMC: at baseline, after one year and after two years, each visit lasting around three hours. If possible, study visits will be scheduled on the same day as their routine appointments to minimize patient inconvenience.

Study burden and risks

There will be no invasive tests during this study. Patients will fill in questionnaires at home and complete neuropsychological tests at the AMC. Filling in questionnaires and completing a neuropsychological test battery costs time and can be experienced as exhausting. If performance on questionnaires and cognitive tests is worse than expected by the Fabry patients or controls this can be experienced as a burden.
Benefits of this study can be: establishing the presence or absence of neuropsychological problems. If any problems are present they can be addressed. In case of neuropsychological problems with impact on wellbeing, Fabry patients or controls will be informed and advised to consult their general practitioner. If there are no evident problems this can be seen as a reassurance of their health status.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
Fabry patients:
* Signed informed consent
* Agreeing to be informed about medically relevant personal test-results by a physician
* Definite diagnosis of FD according to previously developed diagnostic criteria (see protocol: appendix A, Table 1. for diagnostic criteria).

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation in this study:
Fabry patients:
* Unwillingness to participate
* Uncertain FD diagnosis (not fulfilling the criteria mentioned in protocol: appendix A, Table 1)
* Unable to execute approximately two hours of neuropsychological tests
* Medical conditions which make participation in the study not feasible (e.g. other diseases than FD affecting the brain), decided by a medical doctor during screening
* Clinically relevant comorbidities, not attributable to FD, presumably influencing neuropsychological test results
* Severe hearing loss and/or vision loss resulting in inability to complete neuropsychological tests and questionnaires

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-07-2016
Enrollment:	65
Type:	Actual

Ethics review

Approved WMO Date:	26-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2017
Application type:	Amendment
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	NL56773.018.16