Is the presence and development of microvascular disease in type 1 diabetes related to changes in brain structure and cognitive function?

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To answer the question if structural changes of the brain and impairments of cognitive functioning in type 1 diabetes are related to the presence of microvascular disease we will· Compare brain structure (brain volume, white matter lesions) and...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Diabetic complications
Study type	Observational invasive

Summary

ID

NL-OMON29744

Source
ToetsingOnline

Brief title
Microvascular disease and brain structure and function

Condition

- Diabetic complications
- Central nervous system vascular disorders

Synonym
abnormalities of the small blood vessels inside the brain and the relationship with attention, concentration and memory, Microvascular disease of the brain and cognitive functioning

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Diabetes Fonds Nederland; er is subsidie ontvangen voor 3 jaar. De afdeling medische psychologie en het diabetescentrum van het VUmc stellen zich garant voor de kosten van de rest van het onderzoek; het diabetescentrum en de afdeling medische psychologie van het VUmc stellen zich garant voor de kosten van de rest van het onderzoek.

Intervention

Keyword: brain MRI, cognitive functioning, microvascular disease, type 1 diabetes

Outcome measures

Primary outcome

Primary endpoint:

Cognitive function (neuropsychological performance, specifically attention,

mental flexibility and executive functioning) at baseline and at follow-up

Secondary outcome

Secondary endpoints:

Brain volume, white matter lesions at baseline and at follow-up

Study description

Background summary

There is growing evidence that individuals with type 1 diabetes have mild performance deficits in a range of neuropsychological tests compared to non-diabetic controls, but the mechanisms underlying cognitive deterioration in diabetes are poorly understood.
In the past decades, several studies have addressed the effects of recurrent hypoglycemia on cognition. While retrospective studies in adult patients with type 1 diabetes have demonstrated an association between a history of recurrent severe hypoglycemia and a modest degree of cognitive impairment, two large prospective studies did not find such an association. Reanalyses of the DCCT findings confirmed this latter conclusion. Evidence for a damaging effect of chronic hyperglycemia on brain function is now emerging. Hyperglycemia may lead

to accumulation of potentially toxic glucose metabolites, oxidative stress, accelerated formation of advanced glycation end products and microvascular changes in the brain, analogous to peripheral complications of diabetes.
The results of studies using Magnetic Resonance Imaging of the brain (MRI), concerning the severity of cerebral atrophy and white matter lesions in patients with type 1 diabetes, are inconsistent. Problems with study design, including lack of appropriate controls, small sample sizes, and insensitive rating methods, are likely to contribute to these apparent inconsistencies.
It is of great importance to determine whether the observed structural changes in the brain are related to cognition and to assess whether these are associated with disease variables such as chronic hyperglycemia, diabetes duration and/or microvascular damage.

Study objective

To answer the question if structural changes of the brain and impairments of cognitive functioning in type 1 diabetes are related to the presence of microvascular disease we will
· Compare brain structure (brain volume, white matter lesions) and study cognition of type 1 diabetes patients and controls.
· Relate changes in structure and function in type 1 diabetes patients to the progression of microvascular disease.
Besides standardised MRI techniques, we will apply additional, new techniques: diffusion tensor imaging (DTI) and arterial spin labelling (ASL), to enhance our understanding of the potential mechanisms underlying structural brain damage in patients with type 1 diabetes.

Study design

The hypothesis will be tested cross-sectionally and longitudinally (after an interval of four years) in healthy volunteers and type 1 diabetes patients with and without sequelae of longstanding hyperglycemia (i.e. microvascular complications: diabetic retinopathy as a marker of manifest microvascular disease) and a diabetes duration of at least ten years. As indicators of hyperglycemia: HbA1c in blood and Advanced Glycated End products in the cerebrospinal fluid will be measured.

Study burden and risks

Risks for the participants are minimal: for the neuropsychological testing, we will create the most ideal testing situation in which patients are able to perform at their best. We will make sure that there are no distractions, that there will be a non-threatening emotional climate, and we will protect all participants from fatigue. For the ophthalmology examinations, we will use the non-mydriatic Topcon camera. The pupils will require mydriatic eye drops. Following the examination patients will use sunglasses and are not allowed to

drive their car.
Because of its non-invasiveness, the risks of the MRI are minimal. The insulin, and in particular the glucose infusions needed for the hyperinsulinemic glucose clamp may cause some local irritation and in rare cases thrombophlebitis. Adequate rinse procedures with saline and careful insertion of the cannula can prevent these adverse effects in most patients. Participants may suffer some adverse effects of a single lumbar puncture.
Following the LP we will ask the patient to lie down for at least one hour, to reduce the risk of headache.

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

age 18-45 years

right-handedness:
Dutch as a native language

Exclusion criteria

alcohol abuse which is defined as more than 20 gram of alcohol per day,
(history of) use of MDMA, cocaine, heroin, methylphenidate, current regular use of cannabis, or history of regular use on a daily basis for at least 5 years,
current use of benzodiazepines, non-selective beta blockers, oral steroids (>7.5 mg/day),
psychiatric disorder warranting psychotropic treatment (e.g. tranquillisers, anti-depressants)
anaemia or thyroid dysfunction,
history of severe head trauma accompanied by loss of consciousness,
stroke
epilepsy
pregnancy
Parkinson*s disease
inability to undergo MRI (claustrophobia, metal implants, BMI>35),
visual acuity < 0.3 at the last ophthalmologic examination
diabetes duration < 10 years
all other factors that can possibly contribute to cognitive decline or altered cerebral blood flow

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:	Will not start
Start date (anticipated):	01-08-2006
Enrollment:	150

Type:	Anticipated

Ethics review

Approved WMO Date:	23-08-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2012
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	NL11920.029.06