

P-glycoprotein and Amyloid in M. Alzheimer

Published: 10-12-2008

Last updated: 07-05-2024

Goals • Increase the knowledge of the Pgp in the pathophysiology of Alzheimer's disease. • Designing an in vivo method, by positron emission tomography, for measuring Pgp function and A β ; concentration to possibly determine the risk of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Encephalopathies
Study type	Observational invasive

Summary

ID

NL-OMON31892

Source

ToetsingOnline

Brief title

PIB PgP

Condition

- Encephalopathies

Synonym

Alzheimer's disease, dementia

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Neurologie (?)

Intervention

Keyword: amyloid, P-glycoprotein, PIB, verapamil

Outcome measures

Primary outcome

Primary study parameters are the Pgp function, A β accumulation and their correlation in Alzheimer's disease and healthy controls.

Secondary outcome

Not applicable.

Study description

Background summary

Alzheimer's disease (AD) is the most common form of dementia. Since the first presentation of a presenile dementia by Alois Alzheimer the exact pathogenesis is not clarified. Today multiple hypothesis exist of which the amyloid hypothesis receives most support.

The amyloid hypothesis states that beta-amyloid (A β) is the core pathogenic protein. A β is a product of proteolytic splicing of the bigger amyloid precursor protein (APP). APP and A β is found in every cell, but their function is not known.

Because A β is a normal protein it is highly unlikely that the protein itself leads to AD. On the other hand, an enhanced production or diminished clearance could lead to extracellular amyloid plaque as found in AD. Genetic variants of AD are in favor of this theory as in these genetic cases of AD the production of APP is enhanced.

The A β homeostasis is regulated at different levels. There is a peripheral and central A β production, and in absence of any possible degradation or aggregation there is also transport over the blood-brain-barrier (BBB). The transport over the BBB is in part via passive *bulk flow* and in another part via active transporters.

One of these transporters is the P-glycoprotein (P-gp). P-gp protects in physiological circumstances against foreign substances and functions in tissues, such as bowel, liver, kidney and BBB, as a transporter with an excretory and/or barrier function. Recently, it has been pointed out that P-gp functions as efflux transporter for A β . Furthermore, in a study by Vogelgesang et al. an inverse correlation between P-gp and cerebral A β in non-dementing

elderly has been shown. Therefore, a lowered P-gp concentration could in theory well be the reason for A β accumulation in AD.

P-gp is for two reasons of interest. At first, P-gp expression can vary according the polymorphism. Interindividual differences of a susceptibility of lowered P-gp expression and enheightened A β can be explained accordingly. Secondly, Pgp can be modulated pharmacologically. It is known that Pgp function can be lowered or blocked by cyclosporin A, verapamil, erythromycin, fluoxetine, HIV protease inhibitors and different statines. Interestingly, Pgp function can also be enheightened by dexamethason, morfine and riphampicin which could in theory lower the concentration of A β . In a study of Loeb et al. is was pointed out that adminstrition of a riphampicin and doxycycline has a positive effect after 6 and 12 months on a cognitive scale. Possibly modulation of Pgp function can lead to a lesser degree of cognitive decline in AD.

Study objective

Goals

- Increase the knowledge of the Pgp in the pathophysiology of Alzheimer's disease.
- Designing an in vivo method, by positron emssion tomography, for measuring Pgp function and A β concentration to possibly determine the risk of converting from mild cognitive impairment to Alzheimer's disease.

Study design

To test our hypothesis we will be using positron emission tomography and the radiotracers 11C-verapamil and N-methyl-11C-2-(4*-methylaminophenyl)-6-hydroxybenzothiazole, or simply Pittsburgh Compound B (PIB) to respectively measure the expression of P-gp and concentration of A β . Furtermore, a H215O PET scan will performe to facillitate anatomical comparisons and analysis of Pgp function and A β concentration. Every patient undergoes three different PET investigations. At first a H215O PET scan will be performed. In the same session followed by a 11C-PIB scan. One week later, a 11C-verapamil scan is performed. The scans are made in this order to exclude any possible Pgp pump modulation by verapamil.

Study burden and risks

The expect mild to negligible risk of a subcutaneous hematoma is further diminished by working with protocols in the PET center. From experience, it has been shown that PETscan research in Alzheimer's patients is feasible.

Contacts

Public

Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ Groningen
Nederland

Scientific

Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ Groningen
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- Meet the NINCDS-ADRDA criteria for probable Alzheimer's disease
 - Mild form of dementia (MMSE 19-22)
 - Older than 50 years
- Healthy controls do not meet NINCDS-ADRDA or MCI criteria.

Exclusion criteria

- Use of medication that could influence Pgp function, e.g. digoxin, cyclosporin, amiodarone, steroids, quinidin, colchicin, etoposide, antiestrogens and atorvastatin.
- Vascular brain disease or otherwise brain diseases which could influence cerebral metabolism or perfusion.

- Significant kidney or liver disease.
- Neurological symptoms not in agreement with a diagnosis of Alzheimer's disease.
- Pregnancy.
- Prior (excessive) radiation exposure in the same year (including radiological assistants or nuclear medicine employees).

Study design

Design

Study type: Observational invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status: Pending

Start date (anticipated): 01-07-2008

Enrollment: 20

Type: Anticipated

Ethics review

Approved WMO

Application type: First submission

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

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	NL22165.042.08