Accumulation of advanced glycation endproducts in patients with systemic amyloidosis.

Published: 24-11-2016
Last updated: 14-04-2024

To explore whether: 1. Accumulation of AGEs is increased in systemische amyloïdose.2. AGE accumulation is related to the degree of AGE deposition.3. AGE accumulation is related to inflammation, renal function en glycemic status in patients with...

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

Summary

ID

NL-OMON42888

Source
ToetsingOnline

Brief title
AGE in Amyloïdosis

Condition

- Other condition

Synonym
Amyloidosis, Protein folding disease

Health condition

Eiwitvouwziekte

Research involving
Human

Sponsors and support

Primary sponsor: Reumatologie en Klinische Immunologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Advanced glycation endproducts, AL amyloidosis, ATTR amyloidosis

Outcome measures

Primary outcome

Skin autofluorescence as measure of AGE accumulation.

Secondary outcome

Skin autofluorescence will be related to:

- Amyloid load in fat tissue (semi-quantitative scored Congo red-stained

abdominal fat smears)

- SAP-scintigraphy as a mark of amyloid load of the body.

- Levels of C-reactive protein, creatinine and HbA1c.

Study description

Background summary

Amyloidosis is a protein folding disease characterized by deposition of protein fibrils with a β-sheet structure. This structure is responsible for its insolubility and resistance to proteolysis. Is systemic amyloidosis deposition of amyloid in (vital) organs leads to organ dysfunction and, if untreated, eventually leads to death.
Different types of amyloidosis can be distinguished depending on the type of precursor protein of the amyloid fibril. The three most common types of systemic amyloidosis are: AA, AL and ATTR amyloidosis.
In AA amyloidosis the precursor protein is serum Amyloid A protein (SAA), an acute phase reactant. This type of amyloidosis is seen in patients with chronic inflammatory diseases. In AL amyloidosis the precursor protein is a kappa or lambda immunoglobulin light chain. The underlying plasma cell dyscrasia is often very low grade and usually lacks the malignant sheets of immature plasma

cells as seen in multiple myeloma. ATTR amyloidosis is an autosomal dominant hereditary disease caused by various point mutations of transthyretin (TTR), whereas in old age a senile type of ATTR amyloidosis is caused by deposition of wild-type TTR. Transthyretin is almost exclusively produced by the liver and functions as transport protein of thyroid hormone and retinol binding protein.
Advanced glycation end products (AGEs) are proteins or lipids that become non-enzymatically glycated by exposure to sugars under influence of oxidative stress. Increased accumulation of AGEs is seen in patients with diabetes mellitus, patients with renal insufficiency and patients with (chronic) inflammation. AGE have several harmful effects. First, cross-linking of AGEs with proteins in the extracellular matrix results in a decrease of tissue elasticity. Second, AGE-modification may alter protein structure and function. Third, AGEs may modulate the function of cells by interaction with and activation of the receptor for AGEs (RAGE).
Several studies have shown the presence of AGEs in amyloid depositions in patients with ATTR amyloidosis. Recent studies demonstrated that fibrinogen from ATTR patients displays an impaired chaperone capacity, due to differential glycation by methylglyoxal. Glycation of fibrogen thus affects its ability to suppress protein aggregation and amyloid deposition.
Based on these findings it can be hypothesized that AGEs are involved in the pathophysiology of systemic amyloidosis in several ways.

Study objective

To explore whether:
1. Accumulation of AGEs is increased in systemische amyloïdose.
2. AGE accumulation is related to the degree of AGE deposition.
3. AGE accumulation is related to inflammation, renal function en glycemic status in patients with amyloidosis.

Study design

1. AGE accumulation will be studied cross-sectionally in patients with AL and ATTR amyloidosis and healthy age- and sex-matched controls.
Tissue AGEs accumulation can be assessed as skin autofluorescence, following the principles of the AGE-reader, which is a validated and non-invasive technique.

2. Skin autofluorescence will be related to the amyloid load in fat tissue (semi-quantitative scored Congo red-stained abdominal fat smears) and extent of amyloid deposition as assessed using 123I-gelabelde serum amyloïd P component (SAP) scintigraphy.
Abdominal fat smears and SAP scintigraphy are obtained as part of standard clinical care.

3. Skin autofluorescence will be related to levels of C-reactive protein as

measure of inflammation, creatinine as measure of renal function, and HbA1c as measure of glycemic status.

Study burden and risks

Patient burden related to participation in this study exists of measurement of skin autofluorescence using the AGE-reader which takes approximately 10 minutes. This technique is non-invasive, painless and safe. Measurement of skin autofluorescence will be combined with a routine outpatient clinic visit.
Data of patients and controls will be coded. Results of individual patient will not be reported to their physician or medical specialists. The result of AGE-measurement is not disclosed to the patient as AGE-measurement has not yet been validated in patients with amyloidosis and that there are no consequences attached to the outcome.
In addition to the routine blood tests the HbA1c-level will be determined. For this purpose, it is not necessary to draw extra blood. If the patient appears to have diabetes this will be communicated with the patient and his or her physician.
The results of this study can provide insight into the pathophysiology of systemic amyloidosis.

Contacts

Public
Selecteer

Hanzeplein 1
Groningen 9700VB
NL
Scientific
Selecteer

Hanzeplein 1
Groningen 9700VB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

ATTR amyloidosis:
- Written informed consent
- Patient has genotyped TTR mutation with diagnosis of ATTR (congo red positive tissue specimen) or wild-type ATTR amyloidosis (confirmed TTR amyloid by immunohistochemistry without mutation in TTR gene).;AL amyloidosis:
- Written informed consent
- Congo red positive tissue specimen and the presence of a clonal plasma cell dyscrasia. Plasma
cell dyscrasia is diagnosed when a free kappa or lambda light chain is detected in serum of urine
by immunofixation electrophoresis or when a relative excess of cells producing one of the two light
chains is detected in bone marrow.

Exclusion criteria

None

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-12-2016
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	24-11-2016
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	NL58967.042.16