Study Design: Amyloid Pathology In Cognitively Normal Elderly Twins

Nederlands Tweelingen Register

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive neuronal loss and eventually death. Abnormal aggregation of beta amyloid (Aβ) is the first event in AD and is present in 20-40% of cognitively normal elderly (***Figure 1***). After Aβ aggregation neuronal injury develops. The concordance of monozygotic twins for a clinical diagnosis of AD-type dementia is 0.40-0.67. This suggests a major genetic role in the development of AD but also involvement of environmental factors.

Objectives:

1.To determine the **concordance** of Aβ and neuronal injury AD biomarkers and the combination of both in monozygotic twins

2.To analyze the appearance of AD biomarkers in **relation** to cognitive decline and/or diagnosis

3.To test whether discordance is associated with gene expression and **DNA methylation**

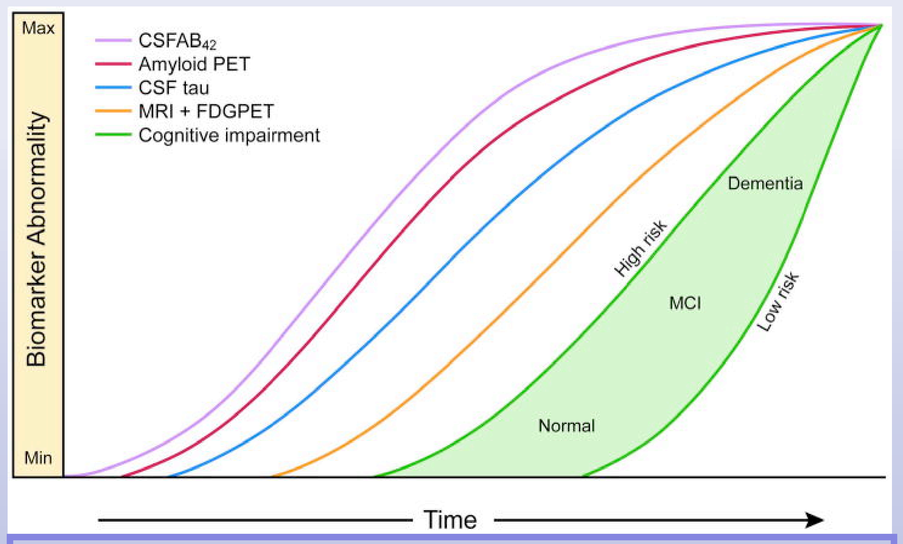

***Figure 1**: Jack et al, Neurology 2013: Revised model of dynamic biomarkers of the AD pathological cascade*

Methods: Cognitive testing and imaging

Longitudinal observational cohort study of 100 monozygotic twin pairs aged 60-100 years from the Netherlands Twin Registry (NTR) (***Table 1***).

After 2 years cognitive testing and questionnaires

Baseline Home Visit	Measurements	Baseline Clinical Visit	Measurements	
Cognitive testing	CANTAB: Paired associate learning, reaction time, rapid visual information processing	MEG	Functional connectivity	
	RAVLT, F-NAME, Fluency, Rey figure	Duplex carotid arteries	Intima-media thickness	Vascular stiffness, stenosis
	Graded Naming Test, TMT A & B, DSST	Blood analysis	Biochemistry, proteomics	RNA, DNA-methylation
	Digit Span, Visual Association Test, NART	CSF analysis	Biochemistry	Aβ, tau, p-tau
Questionnaires	Sleep quality, functional & cognitive activity, quality of life, depression, iADL, nutrition	OCT	Retinal Nerve Fibre Layer thickness	Vascular abnormalities
Physical examination	Blood pressure, weight, length, waist, grip strength, medical history	MRI	Atrophy, vascular damage	T1, FLAIR, ASL, rs-fMRI, DTI, SWI
Neurological examination	Neurological abnormalities	Amyloid-PET	Cerebral amyloid pathology	Dynamic scanning

***Table 1**: Baseline measurements in 200 cognitively normal elderly*

Expected Results: Start December 2014

- Markers amyloid pathology: Aβ in CSF analysis and amyloid-PET scan.
- Markers for neuronal injury: tau & p-tau in CSF, neuropsychological and clinical markers, functional and structural brain connectivity measured by MEG and MRI, brain atrophy by MRI, vascular changes by MRI, retinal imaging and duplex of the carotid arteries

Conclusions

The degree of gene expression and DNA methylation markers will be compared between concordant and discordant twin pairs.

15th Congress of the International Society for Twin Studies – Budapest – 2014