Contribution of age-related-circulatory factors to late-onset Alzheimer’s disease

https://www.neurodegenerationresearch.eu/survey/contribution-of-age-related-circulatory-factors-to-late-onset-alzheimers-disease/

Name of Fellow

Dr. J. Middeldorp,

Institution
Funder

ZonMw

Contact information of fellow
Country

The Netherlands

Title of project/programme

Contribution of age-related-circulatory factors to late-onset Alzheimer's disease

Source of funding information

ZonMw

Total sum awarded (Euro)

€ 200,000

Start date of award

01/12/15

Total duration of award in years

2.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer | Dementia | Aging | Blood | Neuroinflammation | Amyloid |Imaging |Glial cells

Research Abstract

Alzheimer’s disease (AD) is the most common form of dementia in the elderly and the number

of patients with AD is estimated to double over the next 20 years. This will not only be a burden for the patients and their caretakers, but also for society as a whole, considering the demanding health costs. Finding a treatment is now more crucial than ever. Despite considerable research effort over the past decades, there is still no effective therapy that can prevent, halt or reverse disease progression. The identification for new effective drug targets and the development of novel drugs is of utmost priority. In order to find these targets, we have to understand how the disease originates and how we can detect it at an early stage.
Aging is the main risk factor for late-onset AD and several other neurodegenerative diseases, but it remains a mystery why AD largely strikes older adults. It is possible that multiple neuronal abnormalities occur simultaneously in the brain and lead to the progressive disconnection of neuronal networks and the appearance of clinical symptoms. Research on how 'normal aging' of the brain occurs, is shedding light on this question. For example, scientists are learning how age-related changes in the brain may harm neurons and contribute to Alzheimer's damage. Recent work from the Wyss-Coray lab has shown that the aged systemic milieu can modify brain processes and impair cognitive function. In addition, recent work from myself and others in the Wyss-Coray lab has shown that rejuvenating the systemic milieu by treating mice with young blood plasma can improve brain circuits and cognition both in normal aged mice and in a mouse model for AD. So it appears that young circulatory factors can improve specific traits of the disease. However, what causes these changes or if age-related circulatory factors play a role in the origin of the disease is currently unknown.
Based on this research and the fact that old age is the greatest risk factor for late-onset AD I propose to study the contribution of age-related circulatory factors on processes that are known to be affected in AD. In addition I will study if changes in these processes will then lead to dementia.
Over the past decade it has become clear that AD is a multi-factorial disease and that changes take place in the brain many years before the first clinical symptoms. Therefore, detecting early changes is important to be able to determine the origin of the disease. Sophisticated imaging techniques such as Positron emission tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are important tools for this early detection. This can be used for example to follow the accumulation of Amyloid-beta (A-beta) protein in living patients.

For this research proposal I chose to focus on a few characteristics that are important early hallmarks of AD:
– Accumulation of A-beta into senile plaques
– The loss of synapses and neuronal activity
– Neuroinflammation in the brain involving mainly astrocytes and microglia
– Cognitive changes, most importantly memory loss

To answer these questions I will use a mouse model of AD and study the effect of old circulatory factors on brain processes that occur at a young age when disease characteristics just become noticeable. Young AD mice and wildtype controls will be injected with plasma from old wildtype mice (containing age-related circulatory factors) or PBS as a control. In collaboration with Prof. Beekman and his company MILabs I will analyze amyloid deposition and neuroinflammation over time by PET and SPECT imaging in response to intravenous injections of old blood plasma and compare it to PBS-injected mice. Subsequently, the brains of these mice will be analyzed post-mortem for A-beta deposits, loss of synaptic and neuronal activity markers and characteristics of neuroinflammation in glial cells. Furthermore, the Hol lab will teach me how to culture primary astrocytes and microglia from young mice, so I will able to take a close look at

these cell types specifically in vitro. I will treat these glial cultures with different doses of age-related circulatory factors and investigate them for neuroinflammation-related markers and test their phagocytic capacity in relation to synapse elimination and A-beta degradation. In addition I will determine whether these cells secrete more pro-inflammatory after exposure to age-related circulatory factors. Finally, another group of mice will be injected with old plasma or PBS for the assessment of their activity and learning and memory performance.
With this fellowship I could be the first to study the effects of age-related circulatory factors on early AD characteristics.
The proposed research will help to understand the origin and mechanism of AD and the contribution of old age. In the long-term these studies could lead to the discovery of new therapeutic targets for the development of badly needed drugs for the treatment of AD.

Types:
Fellowships

Member States:
Netherlands

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A