# The PARADE study: Pathegenic Antibodies and (Rapidly Progressive) Dementia Syndromes

https://neurodegenerationresearch.eu/survey/the-parade-study-pathegenic-antibodies-and-rapidly-progressive-dementia-syndromes/

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**Funder**

NWO | ZonMw

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**Country**

The Netherlands

**Title of project/programme**

The PARADE study: Pathegenic Antibodies and (Rapidly Progressive) Dementia Syndromes

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NWO | ZonMw

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4.0

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

autoimmune encephalitis | auto-antibodies | dementia | rapidly progressive dementia | immunotherapy

**Research Abstract**
Dementia is one of the major health care challenges of the 21st century. There are currently more than 35 million people affected with dementia worldwide. There is no cure for dementia. We are just starting to understand the etiology, but in many patients the origin of the dementia syndromes is unknown.
Since 2007, several novel autoimmune disorders were identified that associate with cognitive dysfunction, and psychiatric symptoms. These disorders affect patients of all ages and are severe, but responsive to immunotherapy and can recover completely. The associated immune responses are characterized by the presence of pathogenic antibodies against extracellular epitopes of neuronal cell surface proteins or synaptic receptors that are involved in neuronal transmission and excitability, synaptic organization, or clustering of ion channels.
In these disorders, cognitive dysfunction can be the presenting and most prominent symptom, or one of the symptoms. Following the discoveries of those new antibodies, there has been an increase in reports of patients with (rapidly progressive) dementia syndromes and known antibodies, like NMDA receptor or AMPA receptor, who could profit from immunotherapy. However, we have also shown that late-onset autoimmune encephalitis can resemble less progressive dementia syndromes, and is therefore easily missed, leading to diagnosis and treatment delay or even denial. This has led us to hypothesize that a smaller, but not insignificant, part of dementia syndromes are antibody-mediated, especially in those patients with rapidly progressive dementia. Some antibodies are known, but others are to be identified. Although the proportion of patients is unknown, underdiagnosis is highly likely, withholding patients available treatment.

Literature does not offer clinical clues or biomarkers in whom to suspect antibody-mediated dementia. Currently, patients are hardly tested for antibodies, the selection is arbitrary and if tested it is usually only partially, in serum only. The PARADE study will investigate CSF and serum of 700-850 patients with dementia syndromes of all subtypes. These samples will be collected from available cohorts from the Alzheimer Centers, containing over 1000 CSF samples. Due to this surplus we will be able to overrepresent rapidly progressive dementia samples. We will screen by immunohistochemistry, and subsequently test with cell-based assays and immunocytochemistry.
PARADE is designed: 1) to determine the frequency and clinical phenotype of known pathogenic antibodies in patients with dementia syndromes; 2) to identify new antibodies, and their respective clinical phenotypes; 3) to proof pathogenicity of those new antibodies in vitro and in vivo; and, 4) to provide practical, diagnostic guidelines in whom to test for antibodies, and in whom it is unnecessary.

Results from the PARADE study will have immediate effects for patients of today and treating physicians. The minority with known or newly identified antibodies will be offered immunotherapy, providing a chance of (partial or complete) recovery. Implementation of updated diagnostic guidelines due to this research will avoid arbitrariness of testing, offer comfort to physicians through development of unambiguous tests and diminish misdiagnosis or underdiagnosis, providing better care for the patient of tomorrow. PARADE will achieve its objectives by joining the major Dutch Alzheimer Centers (also combined in the Parelsnoer

initiative) with the Dutch laboratory specialized in antibody detection taking advantage of each partners' experience to optimize experimental design. This will be facilitated by the use of proven techniques combined with harmonized and uniformly collected established cohorts (valorisation). As the brain proteins affected by patients' antibodies are involved in these immune-mediated dementias, PARADE will provide a better understanding of the pathophysiological mechanisms disrupted in dementia syndromes.

The PARADE study will result in the identification of novel antibody-mediated dementia syndromes, previously thought to be neurodegenerative, and the development of new, specific diagnostic assays, ready for commercial use (innovation). The health impact will be based on 1) the development of new diagnostic guidelines; 2) improved specific diagnosis, avoiding invasive or unnecessary tests, and 3) options for better therapeutic intervention for a subset of the patient cohort.

**Types:**
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