UKE Paper of the Month May 2014

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Familial Alzheimer's disease–associated presenilin-1 alters cerebellar activity and calcium homeostasis

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ABSTRACT:

Familial Alzheimer's disease (FAD) is characterized by autosomal dominant heritability and early disease onset. Mutations in the gene encoding presenilin-1 (PS1) are found in approximately 80% of cases of FAD, with some of these patients presenting cerebellar damage with amyloid plaques and ataxia with unclear pathophysiology. A Colombian kindred carrying the PS1-E280A mutation is the largest known cohort of PS1-FAD patients. Here, we investigated PS1-E280A-associated cerebellar dysfunction and found that it occurs early in PS1-E208A carriers, while cerebellar signs are highly prevalent in patients with dementia. Postmortem analysis of cerebella of PS1-E280A carrier revealed greater Purkinje cell (PC) loss and more abnormal mitochondria compared with controls. In PS1-E280A tissue, ER/mitochondria tethering was impaired, Ca2+ channels IP3Rs and CACNA1A were downregulated, and Ca2+-dependent mitochondrial transport proteins MIRO1 and KIF5C were reduced. Accordingly, expression of PS1-E280A in a neuronal cell line altered ER/mitochondria tethering and transport compared with that in cells expressing wild-type PS1. In a murine model of PS1-FAD, animals exhibited mild ataxia and re-duced PC simple spike activity prior to cerebellar β-amyloid deposition. Our data suggest that impaired calcium homeostasis and mitochondrial dysfunction in PS1-FAD PCs reduces their ac-tivity and contributes to motor coordination deficits prior to Aβ aggregation and dementia. We propose that PS1-E280A affects both Ca2+ homeostasis and Aβ precursor processing, leading to FAD and neurodegeneration.

STATEMENT:

This paper represents a breakthrough in unravelling the pathophysiology of Alzheimer's Disease. Mutations in Presenilin genes cause early onset hereditary AD. These mutations are thought to alter the function of the "Gamma secretase complex" which is key to the generation of Amyloid beta, an aggregation-prone protein thought to initiate AD. In this collaborative study between UKE scientists and researchers from five different countries in three continents we took advantage of a well documented familial kindred of AD patients carrying a single Presenilin 1 mutation which represents the largest cohort of familal AD in the world. For the first time we showed how abnormal Calcium homeostasis modulated by Presenilin mutation, generates a clinical phenotype of cerebellar ataxia inducing Purkinje cell death, mitochondrial degeneration, abnormal mitochondrial transport and decreased levels of key Calcium proteins. Our data point to a dual role for Presenilin in the pathophysiology of Alzheimer's Disease. This opens several new lines of research and therapeutic approaches to better understand and treat Alzheimer's Disease.

BACKGROUND:

This work was performed at the Institute of Neuropathology in the group of its director, Markus Glatzel, who holds a professorship at UKE since 2005. He has a long term interest in the mechanisms of neurodegeneration in Prion diseases and other dementias. This paper is the seminal work as a Postdoc of Diego Sepulveda-Falla, a Colombian physician-scientist at UKE. His focus of research lies in the molecular biology and pathophysiology of Presenilin mutations.