

Presenilin-1 E280A mutation leads to cerebellar dysfunction via altered Ca²⁺ homeostasis in early onset familial Alzheimer's disease patients

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Research question and background

Familial Alzheimer's disease (FAD) is characterized by autosomal dominant heritability and early onset. Mutations in presenilin-1 (PS1) are found in approximately 80% of cases of FAD, with some of these patients presenting cerebellar damage of unclear pathophysiology. A Colombian kindred carrying the PS1-E280A mutation is the largest known cohort of PS1-FAD patients.

Methods and tissues used

Retrospective clinical data was assessed for determining impact of cerebellar signs and symptoms in demented patients. Histological, ultrastructural and biochemical analyses were performed in cerebella from 5 controls, 10 sporadic AD cases and 12 PS1-E280A FAD cases.

Results and conclusion

We found that PS1-E280A FAD presents with cerebellar dysfunction and that it occurs early in PS1-E280A 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 cerebellar tissue, ER/mitochondria tethering was impaired, IP3Rs and CACNA1A Ca²⁺ channels together with mitochondrial Ca²⁺ dependent transport proteins MIRO1 and KIF5C were reduced. Our data suggest that impaired calcium homeostasis and mitochondrial dysfunction in mutant PS1-FAD Purkinje cells lead to motor coordination deficits prior to A β aggregation and dementia.