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Loss of Calbindin immunoreactivity in the dentate gyrus distinguishes Alzheimer's disease from other neurodegenerative dementias

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HIGHLIGHTS

- We compare Calbindin immunoreactivity in different neurodegenerative diseases.
- We focus on the granule cells of the dentate gyrus.
- Alzheimer's diseased brains show the highest proportion of Calbindin negative cells.
- Progressive loss of Calbindin expression suggests cumulative pathogenetic effects.

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ABSTRACT

Calbindin (Cb) is one of the major Ca^{2+} binding proteins exhibiting neuromodulatory functions such as long-term potentiation (LTP), synaptic plasticity, and memory functions. It is expressed in hippocampal interneurons, pyramidal cells and granule cells of the dentate gyrus (DGCs). Cb mRNA levels remain stable during normal ageing, but decrease in Alzheimer's, Huntington, and Parkinson's disease. A recent study suggested a link between Aβ-induced Alzheimer's disease (AD)-related cognitive deficits and neuronal depletion of Cb. To evaluate whether this is specific for AD, we performed a comparative study of Cb immunoreactivity of DGCs in cases with AD-related neuropathologic change (49), grouped according to the stages of Braak and Braak, BB), Creutzfeldt–Jakob-disease (16), FTLD-tau Pick's disease type (PiD; 5), argyrophilic grain disease (8), and FTLD-TDP types A and B (6). The group of AD cases with BB stages V and VI showed the highest proportion of Cb negative cells in the DGC when compared to all other groups except PiD. The ratio of negative cells correlated significantly with the BB stages. While the total number of DGCs decreased with age in our series, loss of Cb immunoreactivity was shown to be age-dependent only in PiD and FTLD-TDP. We conclude, that late stage AD-neuropathologic change (BB V and VI stages) associates with significantly higher ratios of Cb negative DGCs and this correlates with advanced BB stage. This might suggest an accumulative effect of an epilepsy-like pathway on the Cb expression or the direct influence of local pathological protein deposits on the DGCs.

1. Introduction

Granule cells of the dentate gyrus (DGCs) are glutamatergic excitatory neurons that direct information from the entorhinal cortex to the Ammon's horn, preferentially to pyramidal cells of the CA3 region and mossy cells of the hilus [1]. They are characterized by the expression of Calbindin D28K (Cb), an intracellular protein containing six Ca^{2+} binding domains (EF hands) [12]. Cb is also strongly expressed in CA2 and more diffusely in CA1 pyramidal cells and interneurons in all HC subfields [1,19]. Its Ca^{2+} binding capacity enables neuromodulatory functions such as long-term potentiation (LTP), synaptic plasticity, and memory functions [1].

Most DGCs are born prenatally. During fetal development, they gain Cb-immunoreactivity in an ectal-to-endal and a dorsal-to-ventral fashion, suggesting a role of Cb in maturation of DGCs, which lasts up to 3 years post-partum [1]. During the normal ageing process, hippocampal mRNA levels of Cb remain stable in humans [13], while in Alzheimer's disease (AD), Huntington, and Parkinson's disease, Cb mRNA and protein concentration determined by

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radioimmunoassay are reduced [13,22]. Loss of Cb expression is not associated with reduction of neuronal density or area [20].

AD patients show marked decrease of Cb mRNA levels in hippocampal CA2 and CA1 regions with a strong correlation with the number of neurofibrillary tangles (NFT), but not with the number of senile plaques (SP), duration of disease, age or post mortem delay. In the DG, no difference between AD and controls could be demonstrated by mRNA in situ hybridization [20].

Furthermore, in earlier stages of disease, Cb+ cells seem to have the potential to protect against the formation of NFT or SP [14]. However, high levels of Aβ in the hippocampus are correlated with reduced neuronal Cb levels in DGCs and their dendrites; furthermore in severely demented individuals with AD loss of Cb expression was described [26]. Whether this alteration is specific for AD or appears in other neurodegenerative disease affecting the hippocampus has not yet been evaluated in detail.

2. Materials and methods

2.1. Case selection

84 cases with the neuropathological diagnosis of AD-related neuropathologic change [23] (49, staged according to Braak and Braak, BB [2]), Creutzfeldt–Jakob-disease (16), FTLD-tau Pick's disease type (PiD; 5), argyrophilic grain disease (8), and FTLD-TDP (three Type A and three type B according to the classification system proposed by Mackenzie et al. [18]), were included in this study. Cases were classified following thorough neuropathological examination according to recent diagnostic criteria [16,17]. In all cases, post mortem time ranged between 12 and 24 h. Tissues were immersion fixed in 4% buffered formalin for three to four weeks. Since this study used archival cases and retrospective clinical data, duration of illness was not available in all cases to perform comparisons.

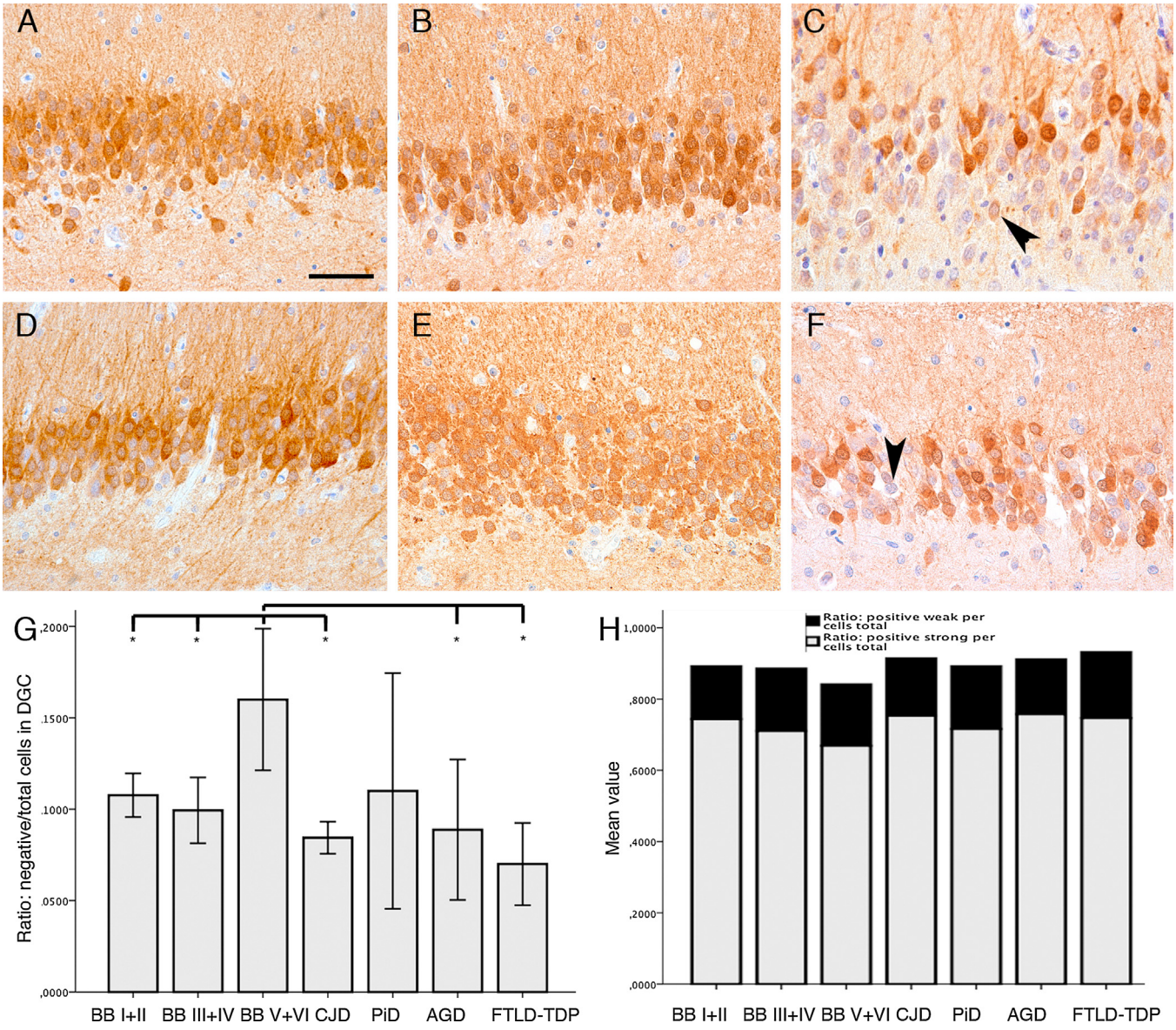

Fig. 1. Immunostaining for Calbindin in the dentate gyrus and ratios of negative and positive cells in different disease groups. Representative photomicrographs of the dentate gyrus granule cell layer (DGC) of a case with Braak and Braak (BB) stage I (A), BB stage IV (B), BB stage VI (C, arrowhead indicates weakly positive cell), compare to other strongly positive cells), Creutzfeldt–Jakob disease (D), FTLD-TDP subtype B (E) and FTLD-tau Pick's disease type (F, arrowhead indicates negative cell). Bar in A represents 50 μm. Mean values (+ standard error in G) of the ratio of negative (G), strongly and weakly positive cells (H) in different disease groups. Asterisk indicates significant difference ($p < 0.05$).