Postmortem neocortical $^3$H-PiB binding and levels of unmodified and pyroglutamate A$\beta$ in Down syndrome and sporadic Alzheimer’s disease

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Abstract

**Background:** Individuals with Down syndrome (DS) have a genetic predisposition for amyloid-$\beta$ (A$\beta$) overproduction and earlier onset of A$\beta$ deposits compared to sporadic late-onset Alzheimer’s disease (AD). Positron emission tomography (PET) with Pittsburgh Compound-B (PiB) detects fibrillar A$\beta$ pathology in living people with DS and AD, but its relationship with heterogeneous A$\beta$ forms aggregated within amyloid deposits is not well understood.

**Method:** We performed quantitative in-vitro $^3$H-PiB binding assays and enzyme-linked immunosorbent assays of fibrillar (insoluble) unmodified A$\beta$40 and A$\beta$42 forms and N-terminus truncated and pyroglutamate-modified A$\beta$NpE3-40 and A$\beta$NpE3-42 forms in postmortem frontal cortex and precuneus samples from 18 DS cases aged 43-63 years and 17 late-onset AD cases aged 62-99 years.

**Result:** Compared to the AD group, the DS group had higher levels of A$\beta$40 and A$\beta$NpE3-40, while the two groups did not differ by A$\beta$42 and A$\beta$NpE3-42 levels, in both the frontal cortex and precuneus. This resulted in lower ratios of A$\beta$42/A$\beta$40 and A$\beta$NpE3-42/A$\beta$NpE3-40 in the DS group compared to the AD group, in both cortical regions. Correlations of A$\beta$42/A$\beta$40 and A$\beta$NpE3-42/A$\beta$NpE3-40 ratios with CAA severity were strong in DS cases, and weak in AD cases. The two diagnostic groups did not differ significantly by $^3$H-PiB binding levels in the frontal cortex or in the precuneus.

**Conclusion:** These results demonstrate that compared to late-onset AD cases, adult DS individuals with similar burden of cortical A$\beta$ plaques have a preponderance of both pyroglutamate-modified A$\beta$NpE3-40 and unmodified A$\beta$40 forms which are associated with greater CAA pathology. Despite the distinct molecular profile of A$\beta$ forms and greater vascular amyloidosis in DS cases, cortical $^3$H-PiB binding does not distinguish between diagnostic groups that are at an advanced level of amyloid plaque pathology. These results underscore the need for development of CAA-selective PET radiopharmaceuticals in order to detect and track the progression of cerebral vascular amyloid deposits in relation to A$\beta$ plaques at the earliest pathology stages in individuals with DS.

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