Neurofilament Light Levels in Cerebrospinal Fluid of the Beagle Dog Increase with Age

C de Rivera[1], J Prenderville[2], R Winters[2], S Thevarkunnel[1], JA Araujo[1]
[1]Transpharmation Inc, Ontario, Canada
[2]Transpharmation Ltd, Dublin, Ireland

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Aims

In humans, neurofilament light (NfL) chain levels and amyloid beta (Aβ) in cerebrospinal fluid (CSF) are used as biomarkers to evaluate disease progression in Alzheimer's disease. Similarly, the aged Beagle dog has previously been shown to have biomarker changes, such as changes in Aβ (Figures 1 and 2) .

The current study sought to further characterize biomarker changes in the aged dog by investigating whether NfL concentrations in canine CSF varies with age.

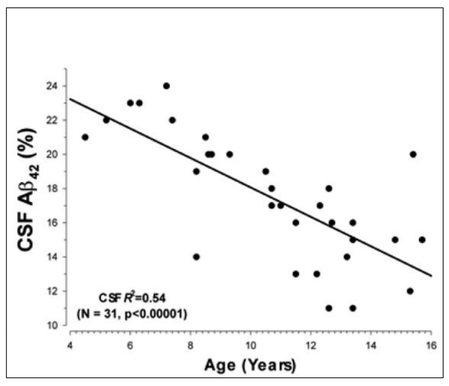

Fig. 1. CSF Ab42 levels in Beagles is correlated with Ab deposition (From Head et al., 2010). In humans, decreased CSF Ab42% is a pathophysiological biomarker of AD evident prior to clinical signs.

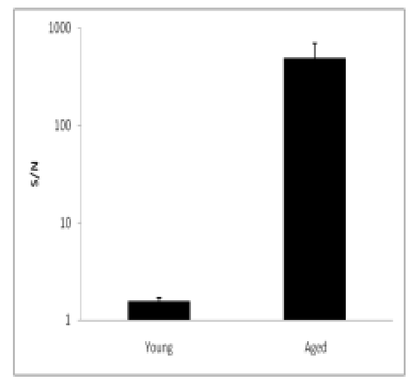

Fig. 2. Oligomeric Ab is exponentially higher in aged dogs, as is variability, compared to young dogs using the A4 assay developed by Amorfix (Toronto, Canada).

Methods

CSF samples from 3 age groups (young, middle-aged, and senior) were quantified for NfL, Aβ42 and Aβ40, using commercially available canine Mesoscale Discovery biomarker kits and analyzed by the MESO QuickPlex SQ. All data were analysed using the GraphPad Prism 9 statistical software. Normality was assessed by the Shapiro-Wilk test. Data was considered non-parametric if it had a p-value less than 0.05 when assessed by these tests. Outliers were removed using ROUT Q=1%. Non-parametric data were analysed by Kruskal-Wallis test by ranks with Uncorrected Dunn's test post hoc. Parametric data were analyzed by One-Way ANOVA followed by Fisher's LSD. An alpha level of 0.05 was used as criterion for statistical significance.

Results

NfL chain levels increased significantly with age in Beagle dogs. The senior and middle-aged groups had significantly higher NfL chain levels in CSF compared to young (Figure 3).

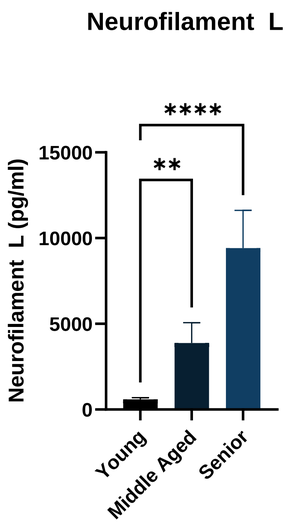

Fig. 3. NfL levels are significantly higher in senior ($p < 0.0001$) and middle-aged dogs ($p < 0.01$) compared to young dogs. All data are presented as mean +/- SEM.

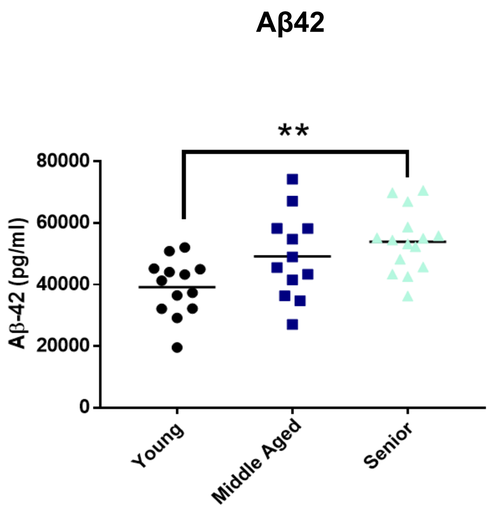

Fig. 4a. Senior dogs have significantly higher Aβ42 levels in CSF compared to young dogs ($p < 0.01$) compared to young. All data are presented as mean +/- SEM.

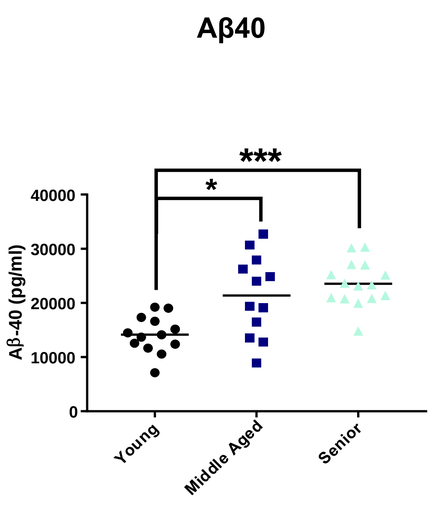

Fig. 4b. Senior dogs ($p < 0.001$) and middle-aged dogs ($p < 0.05$) have significantly higher Aβ40 levels in CSF compared to young All data are presented as mean +/- SEM.

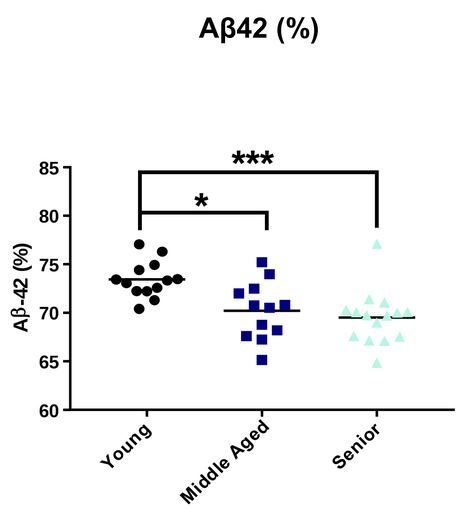

Fig. 4c. The percentage of Aβ42 in CSF is significantly lower in senior dogs ($p < 0.001$) and middle-aged dogs ($p < 0.05$) compared to young dogs. All data are presented as mean +/- SEM.

Aβ also increased with age with Aβ42 concentrations in CSF significantly higher in the senior group compared to young and Aβ40 levels significantly higher in the senior and middle-aged group compared to young animals (Figures 4a and 4b). However, %Aβ42 was significantly lower in the senior and middle-aged group compared to young (Figure 4c).

Conclusions

The age-related increases in NfL chain levels in CSF of Beagle dogs further supports the use of the aged dog as a model of Alzheimer's Disease progression. The decreases in %Aβ42 with age confirms previous findings in the aged dog, which showed %Aβ42 was inversely correlated with amyloid brain load. Additional studies will need to be conducted to determine how changes in NfL relates to other clinically relevant biomarker changes and if there is a correlation with changes in cognitive function that has been previously reported in aged dogs.

CONTACT
christina.derivera@transpharmation.com
www.transpharmation.com