Cerebrospinal Fluid Research

BioMed Central

Oral presentation

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Shunting in AD slows progression of the dementia

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from 51st Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida
Heidelberg, Germany. 27–30 June 2007

Published: 20 December 2007

Cerebrospinal Fluid Research 2007, **4**(Suppl 1):S42 doi:10.1186/1743-8454-4-S1-S42

This abstract is available from: http://www.cerebrospinalfluidresearch.com/content/4/S1/S42

Background

The pathogenesis of Alzheimer's disease (AD) may involve impaired clearance of toxic metabolites, e.g. amyloid-beta peptides (Aβ), from the brain via interstitial fluid (ISF) and cerebrospinal fluid (CSF) circulation, and the blood-brain barrier (BBB). If so, then increasing ISF and CSF circulation may improve CSF Aβ clearance and may slow the progression of AD. We tested this hypothesis in a prospective, randomized, double-blind, placebo-controlled trial of low-flow CSF shunting. Our previously reported analysis using the Generalised Estimating Equations showed no effect of CSF shunting. The present report provides post hoc analyses using linear mixed-effects models fit by maximum likelihood.

Materials and methods

The study group consisted of 164 people with mild to severe AD (baseline Mattis Dementia Rating Scale – MDRS-scores 54–137). We administered the MDRS prior to shunt implantation surgery (baseline, time = 0) and 3, 6, 9, and 12 months post-operatively. We also administered the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) at baseline and 9 months. Linear mixed-effects models fit by maximum likelihood compared the rates of decline for the two groups over the period of 3 to 12 months for the MDRS and 0 to 9 months for the ADCS-ADL. In the MDRS model we co-varied the baseline scores and incorporated random effects and variance functions to adjust for heteroscedasticity when estimating rates of decline.

Results

Rates of decline for both measures were less in the actively shunted AD group. The MDRS rate of decline was 0.54 ± 0.25/month less than the control group ($p = 0.031$). The ADCS-ADL rate of decline was 0.66 ± 0.33/month less then the control group ($p = 0.042$). Variability in the MDRS rate of decline in the active shunt group increased with time, compared to controls ($p < 0.001$).

Conclusion

CSF shunting reduced rates of cognitive and functional decline in patients with mild to severe AD. This supports the hypothesis that impaired CSF clearance of toxic moieties may contribute to the pathogenesis of AD. Mixed effects models of cognitive decline may be more efficient than marginal models, such as the Generalised Estimating Equations. The increased variability in cognitive scores in the group with active shunts may result from the beneficial effects not occurring in some patients, and/or possibly from unwanted side effects in a few individuals. Overall, however, CSF shunting in mild to severe AD was beneficial.