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# Shunting in AD increases ventricular CSF protein levels

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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):S5 doi:10.1186/1743-8454-4-S1-S5

This abstract is available from: http://www.cerebrospinalfluidresearch.com/content/4/S1/S5



## Background

Defects in CSF circulation may impair clearance of toxic metabolites (i.e. amyloid-beta peptides – Aβ), from the brain via interstitial fluid (ISF) and so contribute to pathology in Alzheimer's disease (AD). On this view, constant drainage of CSF via a low-flow ventriculo-peritoneal shunt could facilitate clearance of toxic moieties from ISF and so slow disease progression. We tested this possibility in a prospective, randomized, double-blind controlled, multi-centre trial. We have reported elsewhere that patients with active shunts showed less cognitive decline than controls. Here, we analyse the effects of shunting on CSF protein concentrations in AD patients.

## Materials and methods

The study group consisted of 164 patients with probable AD (NINDS-ADRDA criteria) with mild to severe dementia by Mattis Dementia Rating Scale (MDRS) (baseline MDRS scores of 54–137). We measured total protein concentration in ventricular CSF at shunt implantation (baseline time = 0), and 3, 6, and 9 months post-operatively, using each centre's standard protocol. We analysed changes in protein levels using linear mixed effects models incorporating an exponential variance function to adjust for heteroscedasticity over time. The analyses excluded 25 observations for protein levels, over 70 mg/dl, below 10 mg/dl, missing baseline or 9 month data.

## Results

139 patients had protein data (overall mean 21.8 mg/dl). Protein levels for the control patients decreased by 0.37 mg/dl per month after operation ($t = -2.41$, 125 df, $p = 0.017$) but those in the actively shunted group increased by 0.40 mg/dl per month ($t = 2.16$, 111 df, $p = 0.033$). The contrast between the active shunt and control groups was highly significant ($t = 3.08$, 236 df, $p = 0.003$). The variability of protein levels increased over time in patients with active shunts, but not in controls (LR $\chi^2 = 7.7$, 1 df, $p = 0.006$).

## Conclusion

AD patients with inactive control shunts showed reductions of both cognitive level and CSF protein concentrations. These results suggest the possibility of a progressive failure in mechanism(s) that transport proteins from the ISF to the CSF in AD. Conversely, active CSF shunting increased CSF protein levels in AD patients and helped maintain their cognitive function. These results support the hypothesis that CSF shunting may ameliorate AD by facilitating clearance of toxic moieties from ISF to CSF. The increased variability in protein levels in patients 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.